 EC 98-2761

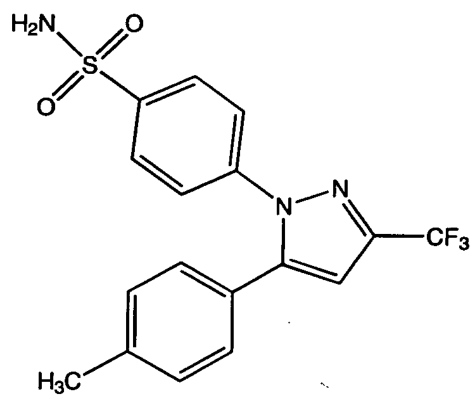
CELECOXIB COMPOSITIONS

Fi ld of the Invention

The present invention relates to oral pharmaceutical compositions and orally deliverable dose units containing celecoxib as an active ingredient, methods of treatment comprising administering such oral pharmaceutical compositions and orally deliverable dose units to a subject in need thereof, and the use of such compositions in the manufacture of medicaments.

Background of the Invention

The compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (also referred to herein as celecoxib) was previously reported in Talley et al., U.S. Patent 5,466,823 which describes and claims a class of 1,5-diaryl pyrazoles and their salts together with processes for the preparation of such compounds. Celecoxib has the structure:



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The 1,5-diaryl pyrazole compounds reported in U.S. Patent 5,466,823 are described as useful in treating inflammation and inflammation-related disorders. U.S. Patent 5,466,823 contains general references to formulations for the administration of these 1,5-diaryl pyrazoles such as tablets and capsules. Talley et al., U.S. Patent 5,760,068 reports a class of 1,5-diaryl pyrazole compounds including celecoxib that are described as selective inhibitors of cyclooxygenase-2 and that can be administered to treat, among other conditions and disorders, pathological conditions associated with rheumatoid arthritis and osteoarthritis.

Penning et al., “Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-

Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib)", J. Med.Chem. 40 (1997):1347-1365, discloses the preparation of a series of sulfonamide-containing 1,5-diarylpyrazole derivatives, including celecoxib, and the evaluation of those derivatives as cyclooxygenase-2 inhibitors.

Simon et al., "Preliminary Study of the Safety and Efficacy of SC-58635, a Novel Cyclooxygenase 2 Inhibitor", Arthritis & Rheumatism, Vol. 41, No. 9, September 1998, pp. 1591-1602, discloses a study of the efficacy and safety of celecoxib in the treatment of osteoarthritis and rheumatoid arthritis.

Lipsky et al., "Outcome of Specific COX-2 Inhibition in Rheumatoid Arthritis", J. Rheumatology, Vol. 24, Suppl. 49, pp. 9-14 (1997), discloses that in patients with rheumatoid arthritis the specific inhibition of cyclooxygenase-2 by celecoxib is sufficient to suppress signs and symptoms of inflammatory disease activity.

EP 863 134 A1 published September 9, 1998 discloses compositions comprising a cyclooxygenase-2 inhibitor, specifically 2-(3,5-difluorophenyl)-3-(4-methyl-sulfonyl)phenyl)-2-cyclopenten-1-one, in combination with microcrystalline cellulose, lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate.

The effective oral administration of celecoxib to a subject has been complicated by the unique physical and chemical properties of the compound, particularly its low solubility, cohesiveness, low bulk density and low compressibility. Celecoxib is unusually insoluble in aqueous media. Unformulated celecoxib is not readily dissolved and dispersed for rapid absorption in the gastrointestinal tract when administered orally in capsule form. In addition, unformulated celecoxib, which has a crystal morphology that tends to be long cohesive needles, typically is cohesive and fuses into a monolithic mass upon compression in a die. Even when blended with other substances, the celecoxib crystals tend to separate from the other substances and agglomerate together during mixing of the composition resulting in a non-uniformly blended composition containing undesirably large agglomerated particles of celecoxib. Therefore, it is difficult to prepare a pharmaceutical composition containing celecoxib that has the desired blend uniformity.

Further, the properties of celecoxib cause handling problems during the preparation of pharmaceutical compositions comprising celecoxib. The low bulk density of celecoxib makes it difficult to process the small quantities required during formulation of the pharmaceutical compositions. In addition, the low compressibility of celecoxib makes it difficult to prepare an orally deliverable dose unit in the form of a tablet. Accordingly, a need exists for suitable oral pharmaceutical compositions and dosage forms comprising celecoxib, particularly orally deliverable dose units.

In particular, a need exists for celecoxib formulations having a greater bioavailability when orally administered than unformulated celecoxib, for example through improvement in one or more pharmacokinetic properties. A need also exists for celecoxib formulations possessing one or more of the folowing characteristics relative to unformulated celecoxib or other compositions:

(1) improved solubility of the pharmaceutical composition;
(2) decreased disintegration times for oral dosage forms;
(3) decreased dissolution times for oral dosage forms;
(4) decreased tablet friability;
(5) increased tablet hardness;
(6) improved safety for oral dosage forms;
(7) improved composition wettability;
(8) improved celecoxib and/or granule particle size distribution;
(9) improved composition compressibility;
(10) improved composition flow properties;
(11) improved chemical stability of the final oral dosage form;
(12) improved physical stability of the final oral dosage form;
(13) decreased tablet or capsule size;
(14) improved blend uniformity;
(15) improved dose uniformity;
(16) improved control of weight variation during encapsulation and/or tableting;
(17) increased granule density for wet granulated compositions;

(18) reduced water requirements for wet granulation;

(19) reduced wet granulation time; and

(20) reduced drying time for wet granulated mixtures.

Such formulations would represent a significant advance in the treatment of cyclooxygenase-2-mediated disorders. The need for such formulations is now satisfied by the invention described below.

Summary of the Invention

There is now provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients.

In one embodiment, a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib characterized by at least one of

(a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;

(b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;

(c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;

(d) a terminal half-life ($T_{1/2}$) not less than about 10 h; and

(e) a maximum concentration (C_{max}) not less than about 200 ng/ml.

In another embodiment, the composition has a relative bioavailability not less than about 50% by comparison with an orally delivered solution containing an equivalent amount of celecoxib.

In still another embodiment, the composition has a distribution of celecoxib particle sizes such that at least 90% of particles are smaller than 200 μm, in the longest dimension of the particles.

The dose units comprising the composition can be in the form of discrete solid articles such as tablets, pills, hard or soft capsules, lozenges, sachets or pastilles; alternatively the composition can be in the form of a substantially homogeneous flowable mass, such as a particulate or granular

solid or a liquid suspension, from which single dose units are measurably removable.

Also provided is a method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering a composition of the invention once or twice a day.

Other features of this invention will be in part apparent and in part pointed out hereinafter.

Brief Description of the Drawings

Figure 1 is a flow diagram illustrating a representative method for the preparation of pharmaceutical compositions of the present invention in the form of capsules.

Figure 2 is a flow diagram illustrating an alternative method for the preparation of pharmaceutical compositions of the present invention in the form of capsules.

Detailed Description of the Invention

Novel pharmaceutical compositions comprising one or more orally deliverable dose units, wherein each dose unit comprises particulate celecoxib in an amount from about 10 mg to about 1000 mg in intimate mixture with the celecoxib, have been discovered that are superior immediate release pharmaceutical compositions. These pharmaceutical compositions are typically immediate release compositions with the intended benefit of providing rapid relief from a cyclooxygenase-2-mediated disorder from which a subject is suffering. These pharmaceutical compositions overcome the insolubility problems normally associated with celecoxib and provide for the effective dissolution, dispersion and absorption of celecoxib in the gastrointestinal tract.

In one embodiment, each orally deliverable dose unit, upon oral administration, provides a time course of blood serum concentration of celecoxib characterized by at least one of the following:

(a) a time to reach a blood serum concentration of about 100 μg/mL that is not greater than about 0.5 hour after administration;

(b) a time to reach a maximum blood serum concentration (T_{max}) of celecoxib that is not greater than about 3 hours after administration, preferably not greater than about 2 hours after administration;

(c) a duration of time wherein the blood serum concentration remains above about 100 μg/mL not less than about 12 hours;

(d) a terminal half life ($T_{1/2}$) that is not less than about 10 hours; and

(e) a maximum blood serum concentration (C_{max}) that is not less than about 100 μg/mL, preferably not less than about 300 μg/mL, and more preferably not less than about 400 μg/mL.

In another embodiment, each orally deliverable dose unit, upon administration, has a relative bioavailability of not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution of celecoxib containing an equivalent amount of celecoxib.

In another embodiment, the novel pharmaceutical compositions comprise one or more orally deliverable dose units comprising celecoxib in an amount from about 10 mg to about 1000 mg wherein the distribution of celecoxib particle sizes in the longest dimension of said particles is such that at least 90% of the particles are smaller than about 200 microns, preferably smaller than about 100 microns, more preferably smaller than about 75 microns, even more preferably smaller than about 40 microns, and still more preferably smaller than about 25 microns. Reduction of the particle size of celecoxib as set forth above generally improves the bioavailability of the celecoxib. In addition or alternatively, each orally deliverable dose unit may contain celecoxib particles having a mean particle size of about 1 micron to about 10 microns, preferably about 5 microns to about 7 microns.

It also has been discovered that milling the celecoxib in an impact mill, such as a pin mill, prior to mixing the celecoxib with the carrier materials is beneficial in overcoming the problems associated with the cohesive nature of celecoxib during blending with the carrier materials. Celecoxib milled using an impact mill is less cohesive than, and does not agglomerate into larger celecoxib particles during blending as readily as, unmilled celecoxib or celecoxib milled using other types of mills, such as fluid energy mills. Without being held to a particular theory, it is hypothesized that the impact milling

modifies the crystal morphology from long needles to a more uniform crystal shape for blending purposes. It also has been discovered that blend uniformity is further improved by wet granulating celecoxib with the carrier materials to prepare the pharmaceutical composition, particularly when the celecoxib starting material used has been impact milled. Impact milling the celecoxib starting material to a particle size as described in the immediately preceding paragraph is particularly desirable.

In yet another embodiment, the novel pharmaceutical compositions comprise one or more orally deliverable dose units comprising celecoxib in an amount from about 10 mg to about 1000 mg and one or more carrier materials selected from diluents, disintegrants, binding agents, wetting agents and lubricants. Preferably, at least one of the carrier materials is a water soluble diluent or wetting agent. The water soluble diluent and wetting agent assist in the dissolution and dispersion of the celecoxib when the pharmaceutical composition is ingested. More preferably, the pharmaceutical composition comprises celecoxib and one or more carrier materials selected from lactose, sodium lauryl sulfate, polyvinylpyrrolidone, croscarmellose sodium, microcrystalline cellulose and magnesium stearate. Additional preferred compositions within this embodiment are described later in this application.

In another embodiment, the pharmaceutical composition comprises a substantially homogeneous flowable mass from which single dose units are measurably removable. Suitable flowable masses include, but are not limited to, particulate or granular solids. Alternatively, the flowable mass can be a liquid suspension having the celecoxib in a solid particulate phase dispersed in an aqueous phase. In preparing such a suspension, use of a wetting agent such as polysorbate 80 or the like may be beneficial. Precipitating the celecoxib from a solvent such as an alcohol, preferably ethanol, also may be beneficial in preparing the suspension. The aqueous phase preferably comprises a palatable vehicle such as water, syrup and fruit juice, for example apple juice.

The compositions of the present invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of

other cyclooxygenase-2 mediated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compositions of the invention would be useful to treat arthritis, including but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compositions of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compositions of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compositions of the invention would be useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like. The compositions would also be useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compositions would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as associated with osteoporosis. The compositions would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" includes partial or total inhibition of the dementia, including Alzheimer's disease, vascular dementia, multi-infarct dementia,

pre-senile dementia, alcoholic dementia, and senile dementia.

The compositions of the invention would be useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compositions would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and liver disease. The compositions would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer.

The compositions above would be useful for, but not limited to, treating and preventing inflammation-related cardiovascular disorders in a subject. The compositions would be useful for treatment and prevention of vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries. The compositions would be useful for, but not limited to, the treatment of angiogenesis-related disorders in a subject. According to the present invention, the compositions can be administered to a subject in need of angiogenesis inhibition. The compositions would be useful for treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

The compositions of the invention would be useful for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophogeal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers. The compositions can also be used to treat the fibrosis which occurs with radiation therapy. The compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the compositions can be used to prevent polyps from forming in patients at risk of FAP.

The compositions of the present invention also would possess anti-inflammatory, antipyretic and analgesic properties similar to conventional non-steroidal anti-inflammatory drugs. These compositions also would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but with a diminished ability to induce some of the mechanism-based side effects. In particular, such compositions would have a reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, a reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, a reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

These compositions would also be useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold,

low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures. In addition, these compositions would inhibit cellular neoplastic transformations and metastic tumour growth and hence can be used in the treatment of cancer, such as cancer of the colon. These compositions also would be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

These compositions also would inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence would be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. They also would be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis), and for treatment of glaucoma.

By virtue of their high cyclooxygenase-2 (COX-2) activity and/or their specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), these compositions would be useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID's) particularly where such non-steroidal antiinflammatory drugs may be contraindicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants. A brief description of the potential utility of cyclooxygenase-2 inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994, and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

Preferred uses for the pharmaceutical compositions of the present invention are for the treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general

surgery pain, post-orthapedic surgery pain, and acute flares of osteoarthritis), the treatment of Alzheimer's disease, and colon cancer chemoprevention.

Besides being useful for human treatment, these compositions are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents and the like. More preferred animals include horses, dogs, and cats.

The present compositions may also be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. More preferred would be combinations with compounds selected from morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone, Tramadol [(+) enantiomer], DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetominophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirfentanil, amitriptyline, DuP631, Tramadol [(-) enantiomer], GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, AXC3742, SNX-111, ADL2-1294, CT-3, and CP-99,994.

Definitions

The term "active ingredient" herein means celecoxib.

The term "excipient" herein includes any substance used as a vehicle for delivery of the active ingredient to a subject, and any substance added to the active ingredient, for example to improve its handling properties or to permit the resulting composition to be formed into an orally deliverable unit dose having the desired shape and consistency. Excipients can include, by way of illustration and not by limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, glidants, substances added to mask a bad taste, substances added to improve appearance of a dosage form, and any other substance conventionally used in the preparation of oral dosage forms.

The term “adjuvant” herein means a substance that, when added to a pharmaceutical composition comprising an active ingredient, increases or otherwise improves the action of the active ingredient.

The term "unit dose" herein refers to an amount of a pharmaceutical composition intended for a single administration to treat a subject suffering from a cyclooxygenase-2-mediated disorder. Each unit dose typically comprises celecoxib plus pharmaceutically acceptable carrier materials.

The term "orally deliverable unit dose" or “unit oral dosage” as used herein means a unit dose of a pharmaceutical composition intended to be administered to the gastrointestinal tract of a subject via the mouth of said subject, and for purposes of the present invention, the unit dose can be in the form of a discrete article such as a tablet or capsule, or a measurable volume of a solution, suspension or the like containing the active ingredient. Nonlimiting examples of dosage forms for administering unit doses are individual tablets, individual gelatin capsules, bulk powders, and liquid solutions, emulsions or suspensions. Treatment of the cyclooxygenase-2-mediated disorder may require periodic administration of unit doses, for example: one unit dose two or more times a day, one with each meal, one every four hours or other interval, or only one per day.

The term "substantially homogeneous," when used herein to describe a pharmaceutical composition that contains a combination of components, means that the components are fully mixed so that the individual components are not separated into discrete layers or do not form concentration gradients within the composition.

The term “bioavailability” generally means the proportion of an administered dose of the active ingredient that is absorbed into the bloodstream. However, as will be clear from the context, the term “bioavailability” is also more specifically used herein to denote $AUC_{(0-\infty)}$ for a specific orally administered composition expressed as a percentage of the $AUC_{(0-\infty)}$ for the active ingredient delivered intravenously at the same dosage rate.

The term “$AUC_{(0-48)}$” means the area under the curve relating blood serum concentration to time after administration from 0 to 48 hours, as

determined using the linear trapezoidal rule, and is expressed in units of (ng/mL)hr.

The term "$AUC_{(0-LQC)}$" means the area under the curve relating blood serum concentration to time after administration from 0 hours to the time of last quantifiable concentration ("LQC"), as determined using the linear trapezoidal rule, and is expressed in units of (ng/mL)hr.

The term "$AUC_{(0-\infty)}$" is calculated as $AUC_{(0-LQC)}$ + LQC/(-b), where LQC is the last quantifiable blood serum concentration and b is the slope from the calculation of $T_{1/2}$ and is expressed in units of (ng/mL)hr.

The term "C_{max}" means the maximum observed concentration, in units of ng/mL.

The term "T_{max}" means the time, in units of hours, after administration at which C_{max} occurs.

The term "$T_{1/2}$" means the terminal half-life, in units of hours, determined via simple linear regression of natural log (ln) concentration vs. time for data points in the terminal phase of the concentration-time curve. $T_{1/2}$ is computed as -ln(2)/(-b).

The term "$C_{max}/AUC_{(0-LQC)}$" means the rate of absorption.

Celecoxib Dosage of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise celecoxib in a daily dosage amount from about 10 mg to about 1000 mg. Preferably, the pharmaceutical compositions comprise celecoxib in an amount of about 50 mg to about 800 mg, more preferably about 75 mg to about 400 mg, and still more preferably about 100 mg to about 200 mg.

Treatment of Specific Conditions and Disorders

The pharmaceutical compositions of the present invention are useful where administration of a cyclooxygenase-2 inhibitor is indicated. It has been found that these compositions are particularly effective in the treatment of, for example, rheumatoid arthritis and osteoarthritis, and for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthapedic surgery pain, and acute flares of osteoarthritis), the treatment of Alzheimer's disease, and colon cancer chemoprevention.

For the treatment of rheumatoid arthritis, the pharmaceutical compositions provide a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 to about 400, and still more preferably about 200 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and about 8.00 mg/kg body weight, more preferably between about 2.00 to about 6.67 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 2.67 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a 100 mg unit oral dosage form twice-a-day is preferred for most patients, but some patients may benefit from administration of a 200 mg unit oral dosage form twice-a-day.

For the treatment of osteoarthritis, the pharmaceutical compositions provide a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 to about 400, and still more preferably about 200 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and about 8.00 mg/kg body weight, more preferably between about 2.00 to about 6.67 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 2.67 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a 100 mg unit oral dosage form twice-a-day or a 200 mg unit oral dosage form once-a-day is preferred.

For the treatment of Alzheimer's disease, the pharmaceutical composition provides a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, still more preferably about 175 to about 400, and still more preferably about 400 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and

about 10.67 mg/kg body weight, more preferably between about 2.00 to about 8.00 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 5.33 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a 200 mg unit oral dosage form twice-a-day is preferred for most patients.

For the treatment of cancer, the pharmaceutical composition provides a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, still more preferably about 175 to about 400, and still more preferably about 400 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and about 10.67 mg/kg body weight, more preferably between about 2.00 to about 8.00 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 5.33 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably two doses per day. Administration of a 200 mg unit oral dosage twice-a-day is preferred for most patients.

In general, the pharmaceutical composition preferably is suitable to provide an average blood serum concentration of celecoxib of at least about 100 ng/mL in a subject over a period of about 24 hours after ingestion of the composition by the subject.

It also has been found that the pharmaceutical compositions of the present invention provide a therapeutic effect as cyclooxygenase inhibitors over an interval of about 12 to 24 hours, preferably about 24 hours, after oral administration.

Unit Dosages

Dosage unit forms of the pharmaceutical compositions may typically contain, for example, a 10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg dose of celecoxib. Preferred dosage unit forms contain about 100 mg or about 200 mg of celecoxib. The dosage unit form may be selected to accommodate the desired frequency of administration used to

achieve the specified daily dosage. The amount of the unit dosage form of the pharmaceutical composition that is administered and the dosage regimen for treating the condition or disorder will depend on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the condition or disorder, the route and frequency of administration, and thus may vary widely.

It has been discovered, however, that a once-a-day or twice-a-day administration regimen to achieve the required daily dosage of the pharmaceutical compositions of the present invention exhibits improved efficacy relative to other administration regimens for the unit dosage forms described in the examples of this application. Accordingly, once-a-day or twice-a-day oral administration is preferred for providing therapeutically or prophylatically effective inhibition of cyclooxygenase-2-mediated disorders.

Preparation of Celecoxib

The celecoxib used in the novel pharmaceutical compositions of the present invention can be prepared in the manner set forth in Talley et al., U.S. Patent 5,466,823, or in Zhi et al., WO96/37476.

Form of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise celecoxib in association with one or more non-toxic, pharmaceutically-acceptable carriers, excipients and adjuvants (collectively referred to herein as "carrier materials" or "excipients") suitable for administration orally. The carrier materials must be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The pharmaceutical compositions of the present invention may be adapted for administration by any suitable oral route by selection of appropriate carrier materials and a dosage of celecoxib effective for the treatment intended. Accordingly, the carrier material employed can be a solid or a liquid, or both, and the composition is preferably formulated as a unit-dose composition, for example, a capsule or tablet, which can contain from about 1% to about 95%, preferably about 10% to about 90%, more preferably about 25% to about 85%, and still more preferably about 30% to about 80%,

by weight of celecoxib. Such pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, comprising admixing the components.

For oral administration, the pharmaceutical composition may contain a desired amount of celecoxib and be in the form of, for example, a tablet, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a liquid, or any other form reasonably adapted for oral administration. Such a pharmaceutical composition is preferably made in the form of a discrete dosage unit containing a predetermined amount of celecoxib, such as tablets or capsules. Such oral dosage forms may further comprise, for example, buffering agents. Tablets, pills and the like additionally can be prepared with or without coatings.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include, for example, lozenges comprising celecoxib in a flavored base, such as sucrose, and acacia or tragacanth, and pastilles comprising celecoxib in an inert base such as gelatin and glycerin or sucrose and acacia.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise, for example, wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

As indicated above, these pharmaceutical compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the celecoxib and the carrier material or carrier materials. In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, encapsulating or shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or

granules optionally mixed with a binding agent, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Carrier Materials

As noted above, the pharmaceutical compositions of the present invention comprise celecoxib in a therapeutically effective amount in combination with one or more pharmaceutically-acceptable carrier materials appropriate for oral administration. Oral dosage forms of the pharmaceutical compositions of the present invention preferably comprise celecoxib in a desired amount admixed with one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents and adhesives, wetting agents, lubricants, anti-adherent agents and/or other carrier materials. More preferably, such compositions are tableted or encapsulated for convenient administration. Such capsules or tablets may be in the form of immediate release capsules or tablets.

The selection and combination of carrier materials used in the pharmaceutical compositions of the present invention provides compositions exhibiting improved performance with respect to, among other properties, efficacy, bioavailability, clearance times, stability, compatibility of celecoxib and carrier materials, safety, dissolution profile, disintegration profile and/or other pharmacokinetic, chemical and/or physical properties. The carrier materials preferably are water soluble or water dispersible and have wetting properties to offset the low aqueous solubility and hydrophobicity of celecoxib. Where the composition is formulated as a tablet, the combination of carrier materials selected provides tablets that may exhibit, among other properties, improved dissolution and disintegration profiles, hardness, crushing strength, and/or friability.

Diluents

The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable diluents as a carrier material. Suitable diluents may include, either individually or in combination,

such diluents as lactose USP; lactose USP, anyhydrous; lactose USP, spray dried; starch USP; directly compressible starch; mannitol USP; sorbitol; dextrose monohydrate; microcrystalline cellulose NF; dibasic calcium phosphate dihydrate NF; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate NF; calcium lactate trihydrate granular NF; dextrates, NF (e.g., Emdex); Celutab; dextrose (e.g., Cerelose); inositol; hydrolyzed cereal solids such as the Maltrons and Mor-Rex; amylose; Rexcel; powdered cellulose (e.g., Elcema); calcium carbonate; glycine; bentonite; polyvinylpyrrolidone; and the like. Said diluent, if present, constitutes about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The diluent or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose and microcrystalline cellulose, either individually or in combination, are preferred diluents. Both diluents are chemically compatible with celecoxib. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a wet granulated composition after the drying step) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides pharmaceutical compositions having suitable celecoxib release rates, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification of the granulation (where wet granulation is employed) and therefore improves blend flow properties.

<u>Disintegrants</u>

The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable disintegrants as a carrier material, particularly for tablet formulations. Suitable disintegrants may include, either individually or in combination, such disintegrants as starches; sodium starch glycolate; clays (such as Veegum HV); celluloses (such as purified cellulose, methylcellulose and sodium carboxymethylcellulose, and carboxymethylcellulose); alginates;

pregelatinized corn starches (such as National 1551 and National 1550); Crospovidone, USP NF; gums (such as agar, guar, locust bean, Karaya, pectin, and tragacanth). Disintegrants may be added at any suitable step during the preparation of the pharmaceutical composition, particularly prior to granulation or during the lubrication step prior to compression. Said disintegrant, if present, constitutes about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 6%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to the pharmaceutical composition of the present invention.

Binding Agents and Adhesives

The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable binding agents or adhesives as a carrier material, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powders to allow for normal processing such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to dissolve upon ingestion. Suitable binding agents and adhesives may include, either individually or in combination, such binding agents and adhesives as acacia; tragacanth; sucrose; gelatin; glucose; starch; cellulose materials such as, but not limited to, methylcellulose and sodium carboxymethylcellulose (e.g., Tylose); alginic acid and salts of alginic acid; magnesium aluminum silicate; polyethylene glycol; guar gum; polysaccharide acids; bentonites; polyvinylpyrrolidone; polymethacrylates; hydroxypropylmethylcellulose (HPMC); hydroxypropylcellulose (Klucel); ethylcellulose (Ethocel); pregelatinized starch (such as National 1511 and Starch 1500). Said binding agent and/or adhesive, if present, constitutes about 0.5% to about 25%, preferably about 0.75% to about 15%, and more

preferably about 1% to about 10%, of the total weight of the composition.

Polyvinylpyrrolidone is a preferred binding agent used impart cohesive properties to the powder blend of the celecoxib formulation. Polyvinylpyrrolidone, if present, preferably constitutes about 0.5% to about 10%, more preferably about 0.5% to about 7%, and still more preferably about 0.5% to about 5% of the total weight of the composition. Polyvinylpyrrolidone viscosities up to about 20 cp may be used although viscosities of about 6 cp or lower are preferred, particularly about 3 cp or lower. Polyvinylpyrrolidone provides cohesiveness to the blend and facilitates the necessary binding to form granules during wet granulation. In fact, pharmaceutical compositions of the present invention comprising polyvinylpyrrolidone, particularly in a wet granulated form, exhibited improved bioavailability relative to other compositions.

Wetting Agents

Celecoxib is largely insoluble in aqueous solution. Accordingly, the pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable wetting agents as a carrier material. Such wetting agents preferably maintain celecoxib in solution and improve the relative bioavailability of the pharmaceutical composition. Suitable wetting agents may include, either individually or in combination, such wetting agents as oleic acid; glyceryl monostearate; sorbitan mono-oleate; sorbitan monolaurate; triethanolamine oleate; polyoxyethylene sorbitan mono-oleate; polyoxyethylene sorbitan monolaurate; sodium oleate; and sodium lauryl sulfate. Wetting agents that are anionic surfactants are preferred. Said wetting agent, if present, constitutes about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the composition.

Sodium lauryl sulfate is a preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 6%, and still more preferably about 0.5 to about 5% of the total weight of the composition.

Lubricants

The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable lubricants and/or glidants as a carrier material. Suitable lubricants and/or glidants may include, either individually or in combination, such lubricants and/or glidants as glyceryl behapate (Compritol 888); stearates (magnesium, calcium, sodium); stearic acid; hydrogenated vegetable oils (e.g., Sterotex); talc; waxes; Stearowet; boric acid; sodium benzoate and sodium acetate; sodium fumarate; sodium chloride; DL-Leucine; polyethylene glycols (e.g., Carbowax 4000 and Carbowax 6000); sodium oleate; sodium benzoate; sodium acetate; sodium lauryl sulfate; and magnesium lauryl sulfate. Said lubricant, if present, constitutes about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression for tablet formulations.

Other carrier materials (such as anti-adherent agents, colorants, flavors, sweeteners and preservatives) are known in the pharmaceutical art and can be used in the preparation of the pharmaceutical compositions of the present invention. For example, iron oxide can be added to the composition to provide a yellow color.

In one embodiment of the present invention, the pharmaceutical composition comprises celecoxib in a desired amount and a binding agent. The composition preferably further comprises one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents, and lubricants. More preferably, the composition comprises one or more carrier materials selected from the group consisting of lactose, sodium lauryl sulfate, polyvinylpyrrolidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Still more preferably, the

composition further comprises one or more of the carrier materials sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose.

In another embodiment, the pharmaceutical composition comprises:

about 1 to about 95 weight percent of celecoxib;

about 5 to about 99 weight percent of a pharmaceutically acceptably diluent;

about 0.5 to about 30 weight percent of a pharmaceutically acceptably disintegrant; and

about 0.5 to about 25 weight percent of a pharmaceutically acceptably binding agent.

In addition, this pharmaceutical composition may optionally comprise about 0.25 to about 15 weight percent of a pharmaceutically acceptably wetting agent; and/or about 0.1 to about 10 weight percent of a pharmaceutically acceptably lubricant. The term "weight percent" as used herein means the weight percent of a specified ingredient based upon the total weight of all ingredients of the composition.

In another embodiment, the pharmaceutical composition comprises:

about 1 to about 95 weight percent of celecoxib;

about 5 to about 99 weight percent of lactose;

about 2 to about 6 weight percent of croscarmellose sodium; and

about 0.5 to about 10 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.25 to about 7 weight percent of sodium lauryl sulfate; about 0.1 to about 10 weight percent of magnesium stearate; and/or about 1 to about 99 weight percent of microcrystalline cellulose.

In another embodiment, the pharmaceutical composition comprises:

about 80 to about 220 mg of celecoxib;

about 30 to about 225 mg of lactose;

about 0.5 to about 25 mg of croscarmellose sodium; and

about 0.5 to about 25 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.5 to about 25 mg of sodium lauryl sulfate; about 0.2 to about 10 mg of

magnesium stearate; and/or about 1 mg to about 70 mg of microcrystalline cellulose.

In still another embodiment, the pharmaceutical composition is in the form of a unit dosage tablet or capsule.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a carrier material or carrier materials in the form of an oral unit dosage suitable for once-a-day or twice-a-day oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib in a desired amount and one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents, lubricants and anti-adherent agents. More preferably, the composition comprises one or more carrier materials selected from the group consisting of lactose, sodium lauryl sulfate, polyvinylpyrrolidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Still more preferably, the composition further comprises one or more of the carrier materials sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions later disclosed in this application.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a pharmaceutically acceptable carrier material or carrier materials that when orally administered to a human patient in need thereof provides a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 hours, preferably at least about 24 hours, after oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib in a desired amount and a binding agent and one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents, lubricants and anti-adherent agents. More preferably, the composition comprises one or more carrier materials selected from the group consisting of lactose, sodium lauryl sulfate, polyvinylpyrrolidone, croscarmellose sodium, magnesium

stearate, and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Still more preferably, the composition further comprises one or more of the carrier materials sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions later disclosed in this application.

Tablets and Capsules

The pharmaceutical compositions of the present invention preferably are tablets, capsules or the like, and more preferably are in the form of immediate release tablets or capsules. These pharmaceutical compositions comprise celecoxib in an appropriate unit dosage of celecoxib sufficient to provide the required daily dosage, that is, such as tablets or capsules orally administered in accordance with a predetermined regimen provide a total daily dosage of about 10 mg to about 1000 mg, more preferably about 50 mg to about 800 mg, still more preferably about 75 mg to about 400 mg, and still more preferably about 100 mg to about 200 mg, of celecoxib. While the amount of celecoxib in such novel compositions preferably is within the ranges previously discussed, the formulations also may be useful for the administration of an amount of celecoxib falling outside of the disclosed dosage ranges.

Celecoxib Particle Size

While the pharmaceutical compositions are effective for a broad range of particle sizes for the initial celecoxib starting material used in the compositions, it has been discovered that reduction of the particle size can improve celecoxib bioavailablity. Accordingly, the D_{90} particle size (90% of the particles in the longest dimension of the particles being smaller than the D_{90} particle size) of the celecoxib preferably is less than about 200 microns, more preferably less than about 100 microns, still more preferably less than about 75 microns, and still more preferably less than 40 microns. For example, as illustrated in Example 11, reducing the D_{90} particle size of the starting material celecoxib from about 60 microns to about 30 microns can

materially improve the bioavailability of the pharmaceutical composition. In addition or alternatively, the celecoxib may have a mean particle size in the range of about 1 micron to about 10 microns, preferably about 5 microns to about 7 microns.

Granulation Particle Size and Flow Properties

While the pharmaceutical compositions of the present invention may be prepared, for example, by direct encapsulation or direct compression, they preferably are wet granulated prior to encapsulation or compression. Wet granulation, among other matters, densifies the compositions resulting in improved flow properties, improved compression characteristics and easier metering or weight dispensing of the final compositions. The particle size of the granulation is not narrowly critical, the important parameters being that the average particle size of the granules preferably allows for convenient handling and processing and, for tablets, permits the formation of a directly compressible mixture that forms pharmaceutically acceptable tablets.

The desired tap and bulk densities of the granulation are normally between about 0.3 g/ml to about 1.0 g/ml.

Dissolution Profile

The compositions of the present invention preferably are immediate release compositions that release at least about 50% of the celecoxib in vitro within about 15 minutes of ingestion. More preferably, they release at least about 60% of the celecoxib in vitro within about 30 minutes of ingestion. Still more preferably, they release at least about 75% of the celecoxib in vitro within about 45 minutes of ingestion.

Disintegration Profile

Carrier materials for immediate release compositions preferably are selected to provide a disintegration time less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less.

Hardness

For tablet formulations, the complete mixture in an amount sufficient to make a uniform batch of tablets is subjected to tableting in a conventional

production scale tableting machine at normal compression pressure (for example, about 1 KN to about 50 KN). Any tablet hardness convenient with respect to handling, manufacture, storage and ingestion may be employed. For 100 mg tablets, hardness is preferably at least 4 kp, more preferably at least about 5 kp, and still more preferably at least about 6 kp. For 200 mg tablets, hardness is preferably at least 7 kp, more preferably at least about 9 kp, and still more preferably at least about 11. The mixture, however, is not to be compressed to such a degree that there is subsequent difficulty in achieving hydration when exposed to gastric fluid.

Friability

For tablet formulations, tablet friability preferably is less than about 1.0%, more preferably less than 0.8%, and still more preferably less than about 0.5%.

In another embodiment, the pharmaceutical composition comprises:

about 25 to about 85 weight percent of celecoxib;
about 5 to about 70 weight percent of lactose;
about 0.5 to about 7 weight percent of polyvinylpyrrolidone; and
about 0.2 to about 5 weight percent of croscarmellose sodium.

In addition, this pharmaceutical composition may optionally comprise about 0.4 to about 6 weight percent of sodium lauryl sulfate; about 0.2 to about 8 weight percent of magnesium stearate; and/or about 0.1 to about 15 weight percent of microcrystalline cellulose. The composition preferably is in the form of a unit dosage capsule.

In another embodiment, the pharmaceutical composition comprises:

about 27 to about 47 weight percent of celecoxib;
about 45 to about 65 weight percent of lactose;
about 0.5 to about 5 weight percent of croscarmellose sodium; and
about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or about 0.25 to about 5 weight percent of magnesium stearate. The composition preferably is in the form of a unit dosage capsule.

In this embodiment, the pharmaceutical composition preferably comprises:

about 32 to about 42 weight percent of celecoxib;

about 50 to about 60 weight percent of lactose;

about 0.5 to about 3 weight percent of croscarmellose sodium; and

about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably comprises:

about 35 to about 39 weight percent of celecoxib;

about 54 to about 57 weight percent of lactose;

about 0.5 to about 2 weight percent of croscarmellose sodium; and

about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 2 to about 4 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 65 to about 85 weight percent of celecoxib;

about 8 to about 28 weight percent of lactose;

about 0.5 to about 5 weight percent of croscarmellose sodium; and

about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or about 0.25 to about 5 weight percent of magnesium stearate. The composition preferably is in the form of a unit dosage capsule.

In this embodiment, the pharmaceutical composition preferably comprises:

about 69 to about 79 weight percent of celecoxib;

about 13.5 to about 23.5 weight percent of lactose;

about 0.5 to about 3 weight percent of croscarmellose sodium; and

about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably comprises:

about 72 to about 76 weight percent of celecoxib;

about 16.5 to about 20.5 weight percent of lactose;

about 0.5 to about 2 weight percent of croscarmellose sodium; and

about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 2 to about 4 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 30 to about 50 weight percent of celecoxib;

about 30 to about 50 weight percent of lactose;

about 0.5 to about 6 weight percent of croscarmellose sodium; and

about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 1 to about 20 weight percent of microcrystalline cellulose; about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or about 0.25 to about 5 weight percent of magnesium stearate. The composition preferably is in the form of a unit dosage tablet.

In this embodiment, the pharmaceutical composition preferably comprises:

about 35 to about 45 weight percent of celecoxib;

about 35 to about 45 weight percent of lactose;

about 1 to about 5 weight percent of croscarmellose sodium; and

about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 5 to about 15 weight percent of microcrystalline cellulose; about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 3 weight

percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably comprises:

about 38 to about 42 weight percent of celecoxib;

about 38 to about 42 weight percent of lactose;

about 1.5 to about 4.5 weight percent of croscarmellose sodium; and

about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 8 to about 12 weight percent of microcrystalline cellulose; about 2 to about 4 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 95 to about 105 mg of celecoxib;

about 145 to about 155 mg of lactose monohydrate;

about 0.5 to about 8 mg of croscarmellose sodium; and

about 2 to about 12 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 3 to about 13 mg of sodium lauryl sulfate; and/or about 0.5 to about 8 mg of magnesium stearate. The composition preferably is in the form of a unit dosage capsule.

In this embodiment, the pharmaceutical composition preferably comprises:

about 98 to about 102 mg of celecoxib;

about 148 to about 152 mg of lactose monohydrate;

about 1.5 to about 4.5 mg of croscarmellose sodium; and

about 4.5 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 6 to about 10 mg of sodium lauryl sulfate; and/or about 1 to about 5 mg of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 195 to about 205 mg of celecoxib;

about 45 to about 55 mg of lactose monohydrate;

about 0.5 to about 8 mg of croscarmellose sodium; and

about 2 to about 12 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 3 to about 13 mg of sodium lauryl sulfate; and/or about 0.5 to about 8 mg of magnesium stearate. The composition preferably is in the form of a unit dosage capsule.

In this embodiment, the pharmaceutical composition preferably comprises:

about 198 to about 202 mg of celecoxib;

about 48 to about 52 mg of lactose monohydrate;

about 1.5 to about 4.5 mg of croscarmellose sodium; and

about 4.5 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 6 to about 10 mg of sodium lauryl sulfate; and/or about 1 to about 5 mg of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 95 to about 105 mg of celecoxib;

about 92 to about 112 mg of lactose monohydrate;

about 2 to about 13 mg of croscarmellose sodium; and

about 1 to about 11 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 20 to about 30 mg of microcrystalline cellulose; about 3 to about 13 mg of sodium lauryl sulfate; and/or about 0.5 to about 7 mg of magnesium stearate. The composition preferably is in the form of a unit dosage tablet.

In this embodiment, the pharmaceutical composition preferably comprises:

about 98 to about 102 mg of celecoxib;

about 100 to about 104 mg of lactose monohydrate;

about 5 to about 10 mg of croscarmellose sodium; and

about 4 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 23 to about 27 mg of microcrystalline cellulose; about 5 to about 10 mg of

sodium lauryl sulfate; and/or about 0.5 to about 4 mg of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 195 to about 205 mg of celecoxib;

about 199 to about 209 mg of lactose monohydrate;

about 10 to about 20 mg of croscarmellose sodium; and

about 7.5 to about 17.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 45 to about 55 mg of microcrystalline cellulose; about 10 to about 20 mg of sodium lauryl sulfate; and/or about 0.5 to about 9 mg of magnesium stearate. The composition preferably is in the form of a unit dosage tablet.

In this embodiment, the pharmaceutical composition preferably comprises:

about 98 to about 102 mg of celecoxib;

about 202 to about 206 mg of lactose monohydrate;

about 13 to about 17 mg of croscarmellose sodium; and

about 10.5 to about 14.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 48 to about 52 mg of microcrystalline cellulose; about 13 to about 17 mg of sodium lauryl sulfate; and/or about 2 to about 6 mg of magnesium stearate.

In still another embodiment, the pharmaceutical composition is capable of releasing in vitro at least 50% of the celecoxib contained in the composition within about 15 minutes of ingestion of the composition.

In still another embodiment, the present invention comprises the pharmaceutical compositions described above in unit dosage form.

In still another embodiment, the present invention comprises the pharmaceutical compositions described above in unit dosage form suitable for once-a-day or twice-a-day administration.

In still another embodiment, the present invention comprises the pharmaceutical compositions described above in immediate release unit dosage form, preferably a tablet or a capsule.

In still another embodiment, the pharmaceutical composition comprises celecoxib wherein the composition is an immediate release oral dosage form,

preferably a tablet or capsule, that releases in vitro at least about 50%, preferably at least about 60%, and more preferably at least about 75%, of the celecoxib contained in the composition within about 45 minutes of ingestion by a subject. Preferably, the composition further comprises one or more pharmaceutically acceptable carrier materials selected from the group consisting of lactose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions set forth above.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a pharmaceutically acceptable carrier material or carrier materials wherein the composition when orally administered to a human patient in need thereof provides a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 hours, preferably at least about 24 hours, after oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib, and one or more carrier materials selected from the group consisting of lactose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions set forth above.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a pharmaceutically acceptable carrier material or carrier materials in the form of an immediate release oral dosage tablet or capsule suitable for once-a-day or twice-a-day oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib and one or more carrier materials selected from the group consisting of lactose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions set forth above.

Method of Treatment

The present invention also is directed to a therapeutic method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated, the method comprising the oral administration of one or more of the pharmaceutical compositions of the present invention to a patient in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to the once or twice a day oral dosages discussed above, but may be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient and the severity of the disease. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

Initial treatment of a patient suffering from a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated can begin with the dosages indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Patients undergoing treatment with the compositions disclosed herein can be routinely monitored by any of the methods well known in the art to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of compounds of the present invention are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of celecoxib exhibiting satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the condition or disorder.

Method For Preparation Of Formulation

The present invention also is directed to methods for the preparation of pharmaceutical compositions comprising celecoxib. In particular, the present invention is directed to methods for the preparation of pharmaceutical compositions comprising celecoxib in unit dosage form, particularly in tablet or

capsule unit dosage form, such that each unit dosage form includes an amount of celecoxib sufficient to provide a therapeutic effect for about 12 to 24 hours. Each unit dosage form preferably contains, for example, from about 100 mg to about 200 mg of celecoxib. Where tablets or capsules are desired, wet granulation, dry granulation or direct compression or encapsulation methods can be employed.

Wet granulation is a preferred method of preparing the pharmaceutical compositions of the present invention. In the wet granulation process, the celecoxib (and, if desired, any of the other carrier materials) is initially milled or micronized to the desired particle size. Although various conventional mills or grinders can be used, impact milling such as pin milling, of the celecoxib provides improved blend uniformity to the final composition relative to other types of milling. Cooling of the celecoxib, for example, using liquid nitrogen, may be necessary during milling to avoid heating the celecoxib to undesirable temperatures. As previously discussed, reduction of the D_{90} particle size to less than about 200 microns, preferably less than about 100 microns, more preferably less than about 75 microns, and still more preferably less than about 40 microns, can materially increase the bioavailability of the celecoxib.

The milled or micronized celecoxib is then blended, for example in a high shear mixer granulator, planetary mixer, a twin-shell blender or sigma mixer, with one or more of the carrier materials. Typically, the drug is blended with the diluent(s), disintegrant(s), binding agent(s) and, optionally, wetting agent(s) in this step although it may be possible to add all or a portion of one or more of the carrier materials in a later step. For example, in tablet formulations where croscarmellose sodium is employed as a diluent, it has been discovered that addition of a portion of the croscarmellose sodium during this blending step (intragranular croscarmellose sodium) and the addition of the remaining portion after the drying step discussed below (extragranular croscarmellose sodium) can improve the disintegration of the tablets produced. In this situation, preferably about 60% to about 75% of the croscarmellose sodium is added intragranularly and about 25% to about 40% of the croscarmellose sodium is added extragranularly. Similarly, for tablet formulations it has been discovered that addition of microcrystalline cellulose

after the drying step below (extragranular microcrystalline cellulose) can improve compressibility of the granulation and hardness of the tablets prepared from the granulation. This blending step of the process preferably comprises the blending of celecoxib, lactose, polyvinylpyrrolidone and croscarmellose sodium. It has been discovered that blending times as short as three minutes can provide a dry powder mixture having a sufficiently uniform distribution of celecoxib. For example, the dry powder mixtures used in the preparation of 100 mg dose capsules (1080 kg total batch size) and 200 mg dose capsules (918 kg total batch size), respectively, had measured relative standard deviation values of 3.6% or less and 1.1% or less, respectively.

Water is then added to the dry powder mixture and the mixture is blended for an additional period of time. The wetting agent used preferably is first combined with the water and mixed for at least 15 minutes, preferably at least 20 minutes, prior to adding the water to the dry powder mixture. The water can be added to the mixture at once, gradually over a period of time, or in several portions over a period of time. The water preferably is added gradually over a period of time. Alternatively, the wetting agent instead can be added to the celecoxib and carrier materials and purified water then can be added to the resulting mixture.

For the illustrative 100 mg dose capsules (1080 kg batch), for example, water addition rates between about 5 to about 25 kg/minute, preferably about 7 to about 20 kg/minute, and still more preferably about 8 to about 18 kg/minute, provide suitable results. An additional period of mixing after the water addition is complete is preferred to ensure the uniform distribution of the water in the mixture. For this batch additional mixing times of about 2 to about 10 minutes, preferably about 3 to about 9 minutes, and more preferably about 3 to about 7 minutes, provide suitable results. The wet granulated mixture of this batch preferably comprises about 2% to about 15% water by weight, more preferably about 4% to about 12%, and still more preferably about 6% to about 10%.

For the illustrative 200 mg dose capsules (918 kg batch), for example, water addition rates between about 5 to about 25 kg/minute, preferably about

7 to about 23 kg/minute, and still more preferably about 8 to about 21 kg/minute, provide suitable results. An additional period of mixing after the water addition is complete is preferred to ensure the uniform distribution of the water in the mixture. For this batch additional mixing times of about 2 to about 15 minutes, preferably about 3 to about 12 minutes, and more preferably about 3 to about 10 minutes, provide suitable results. The wet granulated mixture of this batch preferably comprises about 2% to about 15% water by weight, more preferably about 6% to about 14%, and still more preferably about 8% to about 13%.

The wet granulated mixture preferably is then wet milled, for example with a screening mill, to eliminate large material agglomerations that form as a by-product of the wet granulation operation. If not removed, these agglomerations would prolong the subsequent fluidized bed drying operation and increase the variation with respect to moisture control. For the illustrative 100 mg dose capsules (1080 kg batch) and 200 mg dose capsules (918 kg batch), for example, suitable granulations can be obtained using feed rates up to about 50%, preferably about 2% to about 30%, and still more preferably about 5% to about 20%; and screen sizes of about 1 inch.

The wet granulated/wet milled mixture is then dried, for example, in an oven or a fluidized bed dryer, preferably a fluidized bed drier. If desired, the wet granulated mixture can be extruded or spheronized prior to drying. For the drying process, conditions such as inlet air temperature and drying time are adjusted to achieve the desired moisture content for the dried mixture. It may be desirable to combine two or more granulation sections for this drying step and subsequent processing steps.

For the illustrative 100 mg dose capsules (1080 kg batch) discussed above, dryer inlet temperature can be fixed at 60°C although other inlet temperatures can be used, preferably in the range of about 50°C to about 70°C. Air flow rate can be varied between about 1000 to about 8000 cubic feet per minute, preferably about 2000 to about 7000 cubic feet per minute, and still more preferably about 4000 to about 7000 cubic feet per minute, with a damper opening of about 10% to about 90%, preferably about 20% to about 80%, and still more preferably about 30% to about 70%. Dryer loads of about

35% to about 100%, preferably about 50% to about 100%, and still more preferably about 90% to about 100%, can be used. Average loss on drying under these conditions generally will be between about 0.1% to about 2.0%.

For the illustrative 200 mg dose capsules (918 kg batch) discussed above, dryer inlet temperature can be fixed at 60°C although other inlet temperatures can be used, preferably in the range of about 50°C to about 70°C. Air flow rate can be varied between about 1000 to about 8000 cubic feet per minute, preferably about 3000 to about 7000 cubic feet per minute, and still more preferably about 4000 to about 7000 cubic feet per minute, with a damper opening of about 10% to about 90%, preferably about 20% to about 80%, and still more preferably about 30% to about 70%. Dryer loads of about 35% to about 100%, preferably about 50% to about 100%, and still more preferably about 90% to about 100%, can be used. Average loss on drying under these conditions generally will be between about 0.1% to about 2.0%.

To the extent necessary, the dry granules are then reduced in size in preparation for compression or encapsulation. Conventional particle size reduction equipment such as oscillators or impact mills (such as fitz mills) can be employed. For the illustrative 100 mg dose capsules (1080 kg batch), for example, suitable granulations can be obtained using feed rates of about 20% to about 70%, preferably about 30% to about 60%; mill speeds of about 20% to about 70%, preferably about 40% to about 60%; and screen sizes of about 0.020 inch to about 0.070 inch, preferably about 0.028 inch to about 0.040 inch. For the illustrative 200 mg dose capsules (918 kg batch), for example, suitable granulations can be obtained using feed rates of about 10% to about 70%, preferably about 20% to about 60%; mill speeds of about 20% to about 60%, preferably about 30% to about 50%; and screen sizes of about 0.020 inch to about 0.080 inch, preferably about 0.028 inch to about 0.063 inch. Smaller screen sizes such as 0.028 inch, however, were observed to result in lower throughput of product. Larger screen sizes such as 0.063 inch, however, resulted in an increased population of granules larger in size than 850 microns. Screen sizes around about 0.040 inch appear to eliminate an excessive population of granules larger in size than 850 microns without significantly decreasing throughput.

Variation of the wet granulation and wet milling parameters discussed above can be employed to adjust the granule size distributions. For example, a slight decrease in particle size has been observed as mixing time increases for mixtures containing lower water amounts. It is hypothesized that where the water concentration is too low to fully activate the binder employed, the cohesive forces between the particles are insufficient to survive the shearing forces generated by the mixing blades and granule size attrition rather than growth occurs. To the contrary, increasing the amount of water to fully activate the binder allows the cohesive forces between the particles to survive the shearing forces generated by the mixing blades and granule growth rather than attrition occurs with increased mixing time and/or water addition rate. Variation of the screen size of the wet mill tended to have a greater impact on the granule size than variation of the feed rate and/or mill speed.

The dry granules are then placed in a suitable blender, such as a twin-shell blender, and the lubricant (such as magnesium stearate) and any additional carrier materials are added (such as the extragranular microcrystalline cellulose and extragranular croscarmellose sodium in certain tablet formulations). Blending times depend in part upon the process equipment employed. For the 100 mg dose capsules and 200 mg dose capsules (1080 kg and 918 kg batches) discussed above, blending times of at least about 5 minutes at blender loads ranging from about 15% to about 60% and blender rotational speeds of at least about 10 revolutions per minutes consistently provided a blended material that was extremely uniform with respect to celecoxib concentration. The relative standard deviations measured for unit dose blend samples were 3.9% or less and 2.2% or less for the 100 mg and 200 mg dose capsules, respectively. Where the diluents include microcrystalline cellulose, the addition of a portion of the microcrystalline cellulose during this step has been found to materially increase granule compressiblity and tablet hardness. In addition, increasing the amount of magnesium stearate above about 1% to about 2% was observed to decrease tablet hardness and increase friability and dissolution time.

This blended mixture is then encapsulated (or, if tablets are to be prepared, compressed into tablets to the desired weight and hardness using appropriate size tooling). Conventional compression and encapsulation techniques known to those of ordinary skill in the art can be employed. Suitable results were obtained for capsules by employing bed heights ranging from about 20 mm to about 60 mm, compaction settings ranging from about 0 to about 5 mm, and speeds from about 60,000 capsules per hour to about 130,000 capsules per hour. Weight control of the dose was observed to decrease with either (i) low speed and high compaction, or (ii) high speed and high bed heights. Accordingly, these combinations of parameters preferably are carefully controlled. It was also discovered that slug formation can be minimized or eliminated by using the lowest compaction setting at which capsule weight control can be maintained. Where coated tablets are desired, conventional coating techniques known to those of ordinary skill in the art can be employed.

This combination of unit operations produces granules that are uniform in celecoxib content at the unit dose level, that readily dissolve in vitro, that flow with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that are dense enough in bulk so that the batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

Use in the Preparation of Medicaments

The present invention also is directed to the use of the compositions of the present invention in the preparation of medicaments useful in the treatment and/or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.

The following examples illustrate aspects of the present invention but should not be construed as limitations. The experimental procedures used to generate the data shown are discussed in more detail below. The symbols and conventions used in these examples are consistent with those used in the contemporary pharmaceutical literature. Unless otherwise stated, (i) all percentages recited in these examples are weight percents based on total

composition weight, (ii) total composition weight for capsules is the total capsule fill weight and does not include the weight of the actual capsule employed, and (iii) coated tablets are coated with a conventional coating material such as Opadry White YS-1-18027A and the weight fraction of the coating is about 3% of the total weight of the coated tablet.

Example 1: 100 mg Dose Capsule

A capsule was prepared having the following composition:

Table 1

INGREDIENT	WEIGHT FRACTION (%)	AMOUNT (mg)
Celecoxib	37.04	100
Lactose Monohydrate (NF, Ph Eur)	55.46	149.75
Sodium Lauryl Sulfate (NF, Ph Eur)	3	8.1
Povidone (K29-32 USP)	2.5	6.75
Croscarmellose Sodium (NF, Ph Eur)	1	2.7
Magnesium Stearate (NF, Ph Eur)	1	2.7
Total Capsule Fill Weight	100	270

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2) comprising titanium dioxide (USP), gelatin (NF), and blue ink (SB-6018).

The lactose monohydrate used in each of the examples of the application is commercially available from Formost Farms, Baraboo, Wisconsin. The Ac-Di-Sol brand of croscarmellose sodium used in each of the examples of the application is commercially available from FMC Corporation, Chicago, Illinois. The sodium lauryl sulfate used in each of the examples of the application is commercially available from Henkel Corporation, Cincinnati, Ohio. The Povidone brand of polyvinylpyrrolidone

was used in each of the examples of the application and is commercially available from International Specialty Products. The magnesium stearate used in each of the examples of the application is commercially available from Mallinckrodt Inc., St. Louis, Missouri. The Opadry White YS-1-18027A used to prepare the coated tablets disclosed in the examples of this application is a ready to coat coating formulation commercially available from Colorcon, West Point, Pennsylvania.

Capsule dose strengths between 25 mg to 225 mg can be accommodated by increasing or decreasing the amount of lactose as necessary to provide a total fill weight of 270 mg.

Example 2: 200 Mg Dose Capsule

A capsule was prepared having the following composition:

Table 2

INGREDIENT	WEIGHT FRACTION (%)	AMOUNT (mg)
Celecoxib	74.07	200
Lactose Monohydrate (NF, Ph Eur)	18.43	49.75
Sodium Lauryl Sulfate (NF, Ph Eur)	3	8.10
Povidone (K29-32 USP)	2.5	6.75
Croscarmellose Sodium	1	2.7
Magnesium Stearate (NF, Ph Eur)	1	2.7
Total Capsule Fill Weight	100	270

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2) comprising titanium dioxide (USP), gelatin (NF), and blue ink (SB-6018).

Exampl 3: 100 mg Dos Tabl t

Tablets were prepared having the following composition:

Table 3

INGREDIENT	AMOUNT (mg/tablet)	WEIGHT FRACTION (%)	AMOUNT/ SECTION (kg/batch)
Celecoxib	100	40	6.40
Lactose Monohydrate (NF)	101.88	40.75	6.52
Sodium Lauryl Sulfate (NF)	7.5	3	0.48
Povidone (K29/32, USP)	6.25	2.5	0.40
Croscarmellose Sodium (Type A, NF)	7.5	3	0.48
Microcrystalline Cellulose (Avicel PH-102, NF)	25	10	1.60
Magnesium Stearate (NF)	1.88	0.75	0.12
Total	250.01	100	16
Opadry White YS-1-18027A	7.50		

The tablets prepared were 0.2100 inch X 0.4650 inch modified oval shaped tablets.

The Avicel brand of microcrystalline cellulose was used in the preparation of the tablets of Examples 3 and 4 and is commercially available from FMC Corporation, Philidelphia, Pennsylvania.

Tablet dose strengths between 25 mg to 225 mg can be accomodated by increasing or decreasing the amounts of celecoxib and each of the carrier materials described above so as to maintain the same weight fractions exemplified above.

Exampl 4: 200 Mg Dos Tabl t

Tablets were prepared having the following composition:

Table 4

INGREDIENT	AMOUNT (mg/tabl t)	WEIGHT FRACTION (%)	AMOUNT/ SECTION (kg/batch)
Celecoxib	200	40	6.40
Lactose Monohydrate (NF)	203.75	40.75	6.52
Sodium Lauryl Sulfate (NF)	15	3	0.48
Povidone (K29/32, USP)	12.5	2.5	0.40
Croscarmellose Sodium (Avicel PH-102, NF)	15	3	0.48
Microcrystalline Cellulose (Type A, NF)	50	10	1.60
Magnesium Stearate (NF)	3.75	0.75	0.12
Total	500	100	16
Opadry White YS-1-18027A	15.0		

The tablets prepared were 0.2750 inch X 0.4960 inch modified capsule shaped tablets.

Example 5: Disintegration Tests

Six identical tablets were separately placed into one of six tubes having a wire mesh screen bottom in a disintegration basket. A water bath was preheated to 37°C ± 2°C and maintained at that temperature for the duration of the disintegration test. A 1000 mL beaker was placed in the water bath. The beaker was filled with a sufficient amount of water to ensure that the wire mesh screen of the tubes would remain at least 2.5 cm below the water surface during the test. The disintegration basket was inserted in the water at time = 0 minutes and repeatedly raised and lowered until the test was complete while maintaining the wire mesh screen of the tubes at least 2.5 cm below the water surface. Disintegration time for each tablet was the time at

which the very last portion of the tablet passed through the screen at the bottom of the tube. The mean results for the uncoated tablets of Examples 3 and 4 are reported in Table 5.

Table 5

TABLET	DISINTEGRATION TIME (MINUTES)
Example 3: 100 mg Dose Tablet (Uncoated)	4 minutes, 35 seconds
Example 4: 200 mg Dose Tablet (Uncoated)	7 minutes, 40 seconds

<u>Example 6: Dissolution Tests</u>

The apparatus of U.S.P. II (with paddles) was used to determine the dissolution rate of the capsules of Examples 1 and 2 and the uncoated tablets of Examples 3 and 4. A 1000 mL 1% sodium lauryl sulfate/0.04M Na_3PO_4 (pH = 12) solution was used as the dissolution fluid. The solution was maintained at a temperature of 37°C ± 5°C and stirred at 50 rpm during the test. Twelve identical tablets or capsules were tested. The 12 tablets or capsules were each separately placed in one of 12 standard dissolution vessels and time = 0 minutes. At time = 15, 30, 45 and 60 minutes, a 5 mL aliquot of solution was removed from each vessel. The sample from each vessel was filtered and the absorbance of the sample measured (UV spectrophotometer; 2 mm pathlength quartz cell; 243 nm or wavelength of UV maxima; blank: dissolution medium). Percent dissolution was calculated based on the measured absorbances. The mean results of the dissolution tests are reported in Table 6.

Table 6

DOSAGE FORM	% DISSOLVED			
	15 minutes	30 minutes	45 minutes	60 minutes
Example 1: 100 mg Dose Capsule	89	99	100	100
Example 2: 200 mg Dose Capsule	55	82	89	92
Example 3: 100 mg Dose Tablet	81	93	94	95
Example 4: 200 mg Dose Tablet	60	96	98	98

Example 7: Particle Size Analysis

Table 7A shows the results of a particle size sieve analysis of the wet granulated pharmaceutical compositions of Examples 1 and 2, respectively, prior to encapsulation. The column entitled "Percent Retained On Screen" reports the percent of the total batch having a particle size larger than the indicated sieve size.

Table 7A

SIEVE SIZE (MICRONS)	EXAMPLE 1 (100 mg DOSE CAPSULE): PERCENT RETAINED ON SCREEN		EXAMPLE 2 (200 mg DOSE CAPSULE): PERCENT RETAINED ON SCREEN	
	Lower Limit	Upper Limit	Lower Limit	Upper Limit
850	0	1.3	1.1	10.7
425	2.8	14.9	4.3	25.4
250	10.0	25.5	10.8	35.4
180	15.3	39.0	17.3	39.2
106	32.5	64.5	35.2	58.2
75	37.1	77.5	39.5	71.8
0	100	100	100	100

Table 7B shows the results of a particle size sieve analysis of the wet granulated pharmaceutical compositions of Examples 3 and 4, respectively,

prior to compression into the tablets. The column entitled “Percent of Batch” reports the percent of the total batch having a particle size between the indicated sieve size and the next smaller sieve size indicated. The column entitled “Cumulative Percent of Batch” reports the percent of the total batch having a particle size larger than the indicated sieve size.

Table 7B

SIEVE SIZE (MICRONS)	EXAMPLE 3 (100 mg DOSE TABLET)		EXAMPLE 4 (200 mg DOSE TABLET)	
	Percent of Batch	**Cumulative Percent of Batch**	**Percent of Batch**	**Cumulative Percent of Batch**
840 (20 mesh screen)	1	1	0.79	0.79
420 (40 mesh screen)	24.6	25.6	24.85	25.64
250 (60 mesh screen)	18.4	44	19.13	44.77
177 (80 mesh screen)	9.6	53.6	11.05	55.82
149 (100 mesh screen)	6.6	60.2	6.9	62.72
105 (140 mesh screen)	11.6	71.8	11.44	74.16
74 (200 mesh screen)	8.8	80.6	8.28	82.45
Fines	19.4	100	17.55	100

Example 8: Bulk Density Analysis

Table 8 shows the results of a bulk density analysis of the wet granulated pharmaceutical compositions of Examples 1, 2, 3 and 4 prior to encapsulation or compression into tablets:

Table 8

COMPOSITION	BULK DENSITY (g/mL^3)	TAPPED DENSITY (g/mL^3)	LOSS ON DRYING (%)
Example 1: 100 mg Dose Capsule	0.77	1.02	0.6
Example 2: 200 mg Dose Capsule	0.61	0.96	0.5
Example 3: 100 mg Dose Tablet	0.73	0.87	1.37
Example 4: 200 mg Dose Tablet	0.72	0.86	1.4

Example 9: Tablet Analysis Program

Table 9 shows the results of the tablet analysis program ("TAP analysis") for a sampling of tablets of having the composition of the tablets of Examples 3 and 4.

Table 9

TABLETS TESTED (N = 10)	AVERAGE WEIGHT (mg)	AVERAGE THICKNESS (inches)	HARDNESS (kP)
Example 3: 100 mg Dose Tablet	248	0.1605	8.2
Example 4: 200 mg Dose Tablet	500	0.2177	14.6

Example 10: Friability Test

Tablets collectively weighing 12 g were placed in a rotating drum. Extraneous dust was first removed from the drum and the tablets. The drum was started and rotation continued for ten minutes at a minimum of 25 rotations per minute. The rotation of the drum was stopped and the tablets removed. Loose dust on the tablets as well as any broken tablets were removed and the intact tablets were weighed. The percent loss of the test samples from Examples 3 and 4 was calculated and is reported below in Table 10.

Table 10

TABLETS	PERCENT LOSS
Example 3: 100 mg Dose Tablet	0.33
Example 4: 200 mg Dose Tablet	0.16

Example 11-1: Bioavailability In A Dog Model

Healthy female beagle dogs weighing between nine to thirteen pounds received the following single doses of celecoxib: (1) an intravenous infusion of 0.5 mg/kg body weight of celecoxib followed by a second intravenous infusion of 5.0 mg/kg body weight of celecoxib; (2) 5 mg/kg body weight celecoxib in the form of an oral solution; and (3) 5.0 mg/kg body weight of neat celecoxib in the an oral capsule. The vehicle for the intravenous and oral solution doses was PEG-400:water (2:1). Each intravenous infusion was given over a period of 15 minutes with 15 to 30 minutes separating the two infusions.

Multiple blood samples were collected from each animal by venipuncture or indwelling catheter into heparinized tubes. The mean results for the dogs tested are reported in Table 11-1 below.

Table 11-1

Pharmacokinetic Parameter	Intravenous Infusion (0.5 + 5.0 mg/kg body weight)	Oral Solution (5.0 mg/kg body weight)	Capsule (5.0 mg/kg body weight)
C_{max} (μg/mL)	6.95	2.19	0.517
T_{max} (hours)	Not applicable	0.5	3.0
$AUC_{0-\infty}$ (μg•hr/mL)	31.2	16.2	4.80
Clearance (mL/min•kg)	3.08	5.14	17.4
Volumes of Distribution (mg/kg)	2420	Not applicable	Not applicable
$T_{1/2}$ (hour)	8.84	9.15	11.8
Bioavailability (%)	Not applicable	57.1	16.9

Exampl 11-2: Effect Of Formulating Variabl s On R lative Bioavailability, W tting P rformance, And Disint grati n P rformanc

The effect of such formulation parameters as drug particle size, increased concentrations of surfactant, pH, and dispersibility were evaluated

relative to oral solutions and unformulated drug in a capsule in a dog model. The effect of micronizing celecoxib (mean particle size 10-20 microns) was tested in formulation A. The combined effect of micronization, added surfactant (sodium lauryl sulfate), and increased micro-environmental pH ($Na_3PO_4.12H_2O$) was tested in formulation B. The effect of bringing the surfactant (Tween 80) into intimate contact with celecoxib (co-precipitating vs. simple dry mixing) was tested in formulation C. The effect of further reducing particle size (approximating one micron) and dispersing the particles in a suspension was tested in formulation D. A solution of celecoxib (formulation E) was included as a reference. In addition, data from Example 11-1 for unmilled, unformulated celecoxib in a capsule (formulation F) is also included as a reference. The specific compositions of formulations A, B, C, D, E and F are summarized in Table 11-2A.

Table 11-2A

INGREDIENT	WEIGHT FRACTION (%)					
	A	B	C	D	E	F
celecoxib (micronized)	25	25				
celecoxib/tween 80[(1)]			25			
celecoxib (dispersed)[(2)]				100		
celecoxib (solution)[(3)]					100	
celecoxib (unmilled)						100
sodium lauryl sulfate	2	25				
Avicel 101	73	25	75			
$Na_3PO_4H_2O$		25				
Total	100	100	100	100	100	100

[(1)] Precipitated from ethanol solution using 5% Tween 80 in water solution as an antisolvent.

[(2)] Prepared as a suspension by ball-milling the drug in a slurry of polysorbate 80 and polyvinylpyrollidone until particles were approximately one micron in diameter as estimated by microscopy.

[(3)] Solution in polyethylene glycol 400:water (2:1 v/v).

The formulations were administered to groups of three male and three female dogs. Group 1 dogs were administered 5 mg per kg body weight celecoxib in solution formulation E and in capsule formulations A and B in a nonrandomized crossover design. Group 2 dogs were administered 5 mg per kg body weight celecoxib in capsule formulation C and in suspension D in a capsule in a nonrandomized crossover design. Plasma samples were collected over a 24-hour period and analyzed for celecoxib with an HPLC method. A 5 mg per kg body weight dose of celecoxib was administered to dogs in the capsule formulation F study.

The results of the study (Tables 11-2B, 11-2C1 and 11-2C2) indicated that decreasing the particle size (A) or increasing the wetting (C) increased the availability (as measured by $AUC_{(0\text{-}24\ hrs)}$) of celecoxib compared to earlier studies of unformulated drug in a capsule. The availability of celecoxib was greater from the PEG:H_2O solution and the suspension (D). The availability from the suspension was approximately the same as from the solution and indicated that celecoxib availability can be improved by celecoxib particle size control (such as pin milling of celecoxib), increased wetting of the celecoxib (such as by including sodium lauryl sulfate in the granulating fluid) and improved dispersibility (such as by including croscarmellose sodium in the granulation). The bioavailability data contained in Tables 11-2C1 and 11-2C2 for each formulation represent the bioavailability of that formulation as a percent of the bioavailability experimentally measured for intravenous administration of celecoxib.

Table 11-2B

Time (hours)	Bl od Serum C l coxib Concentration (mg/mL)					
	A[1]	B[1]	C	D[1]	E	F
0	0	0	0	0	0	0
0.5	0.0143	0.247	0.0635	0.453	0.824	0.205
1.0	0.244	0.228	0.443	0.826	0.820	0.333
2.0	0.318	0.138	0.717	0.865	0.604	0.262
3.0	0.189	0.0860	0.492	0.741	0.517	0.517
4.0	0.145	0.0707	0.384	0.576	0.413	0.234
6.0	0.107	0.0664	0.233	0.354	0.286	0.197 (measured at 7.0 hours)
8.0	0,0828	0.0624	0.160	0.234	0.187	--
12.0	0.0939	0.0431	0.0865	0.142	0.0802	--
24.0	--	0.0404	0.0408	0.0394	0.0159	--

[1] Micronized celecoxib.

Table 11-2C1

Pharmacokinetic Parameter	Pharmacokinetic Parameter Value For Female Dogs Tested					
	A[1]	B[1]	C	D[1]	E	F
C_{max} (mg/mL)	0.36 ±0.06	0.25 ± 0.07	0.79 ± 0.19	1.01 ± 0.27	0.84 ± 0.24	0.5
T_{max} (hours)	1.3 ± 0.2	0.7 ± 0.2	1.5 ± 0.3	1.7 ± 0.44	0.67 ± 0.18	3.0
Bioavailability (%)	31.2 ± 2.9	24.9 ± 1.4	46.3 ± 9.5	69.5 ± 9.6	62.4 ± 9.4	16.9

[1]Micronized celecoxib.

Table 11-2C2

Pharmacokinetic Param t r	Pharmacokin tic Param t r Value For Male Dogs Test d					
	A[1]	B[1]	C	D[1]	E	F
C_{max} (mg/mL)	0.52 ±0.11	0.45 ± 0.18	0.64 ± 0.26	0.83 ± 0.33	1.52 ± 0.20	0.5
T_{max} (hours)	5.3 ± 3.3	3.3 ± 1.3	1.5 ± 0.5	5.7 ± 3.42	1.5	3.0
Bioavailability (%)	49.4 ± 12.0	54.2 ± 13.1	42.9 ± 13.1	87.5 ± 20.6	89.4 ± 4.5	16.9

[1]Micronized celecoxib.

Various formulations containing sodium lauryl sulfate (0-5% w/w) and croscarmellose sodium (0-5%) were screened for relative wettability and disintegration tendency. Relative wettability was estimated by measuring the time required for water to penetrate a column of granulated material prepared from each formulation. Disintegration tendency was determined by measuring the weight of granulated material retained on a #20 (850 mm) screen after soaking the material in 37°C water for 5 minutes. The specific compositions of formulations A through H evaluated are summarized in Table 11-2D.

Table 11-2D

Formulation	**WEIGHT FRACTION (%)**							
	A[(1)]	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Celecoxib	74.7	74.7	74.7	74.7	74.7	74.7	74.7	74.7
Lactose	15.8	15.8	21.8	19.8	17.8	15.8	17.8	11.8
Polyvinyl-pyrrolidone	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium Lauryl Sulfate	3.0	3.0	0.0	1.0	1.0	1.0	3.0	5.0
Ac-di-sol	3.0	3.0	0.0	1.0	3.0	5.0	1.0	5.0
Magnesium Stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

(1)Sodium lauryl sulfate was added as a dry powder

Results are summarized in Table 11-2E. Penetration tests were done in triplicate. Disintegration tests were done in duplicate. Results of the penetration study indicated that wet application of sodium lauryl sulfate (Formulation B) was superior to dry application (formulation A) and that formulations containing 3 to 5 weight percent sodium lauryl sulfate (formulations B, G, and H) were superior to those with lesser amounts of sodium lauryl sulfate (formulations C through F). Formulations containing 3% sodium lauryl sulfate (formulations B and G) were similar to those containing 5% (formulations H). Results of the disintegration study indicated that complete disintegration could be achieved with sodium crosscarmellose concentrations as low as 1% (formulation G) at surfactant concentrations of 3%. Complete disintegration could also be achieved with higher amounts of disintegrant (formulations B, F, and H) regardless of surfactant concentration. Formulation G exhibited both superior penetration and complete disintegration with the minimum amount of excipient required.

Table 11-2E

Formulation	% Sodium Lauryl Sulfate/% Ac-di-sol	Penetration Time (n=3)	Disintegration (n=2)
A[(1)]	3/3	>18 hours	0.1-0.5%
B	3/3	5-60 minutes	none detected
C	0/0	>4 to >18 hours	20-26%
D	1/1	>4 to >18 hours	10-13%
E	1/3	2 to 4 hours	4-6%
F	1/5	1 to 4 hours	none detected
G	3/1	10 to 40 minutes	none detected
H	5/5	10 to 55 minutes	none detected

(1) Sodium lauryl sulfate was added as a dry powder

Example 12

The following formulations were evaluated for wetting effects and mixture uniformity:

Table 12

INGREDIENT	**WEIGHT FRACTION (%)**							
	Lactose Dry Blend		**Microcrystalline Cellulose Dry Blend**		**Polyvinyl-pyrrolidone Granulation**[1]		**Polysorbate 80 Granulation**[2]	
Celecoxib	5	60	5	60	5	60	5	60
Lactose	94.5	39.5	--	--	92	37	93.5	38.5
Microcrystalline Cellulose	--	--	94.5	39.5	--	--	--	--
Polysorbate 80	--	--	--	--	--	--	1.0	1.0
Povidone (K29-32)	--	--	--	--	2.5	2.5	--	--
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

[1] In this formulation polyvinylpyrrolidone was added to the blend as a dry powder prior to granulation with water.

[2] In this formulation celecoxib and lactose were granulated with an aqueous solution of polysorbate 80.

The 5% celecoxib blends exhibited better blend homogeneity than the 60% celecoxib blends. The measured relative standard deviations for the 5% celecoxib blends ranged from 0.4% to 3.5% while the measured relative standard deviations for the 60% celecoxib blends ranged from 4.7% to 6.3%. In addition to being less homogeneous, the 60% celecoxib blends contained relatively large granules (greater than 420 microns) that were superpotent (containing 124% to 132% higher concentrations of celecoxib relative to other granules).

Four similar formulations were prepared containing 25% celecoxib loading instead of 5% or 60% celecoxib loading as above. The bioavailability of these formulations was evaluated in a dog model. The polyvinylpyrrolidone wet granulation formulation exhibited the highest bioavailability (about 74%).

Example 13

Capsules having the following formulations were prepared and evaluated:

Table 13A

INGREDIENT	**AMOUNT (mg)**		
	5 mg Dose Capsule	**20 mg Dose Capsule**	**100 mg Dose Capsule**
Celecoxib	5	20	100
Lactose	92	77	61.9
Povidone (K29-32)	2.5	2.5	4
Magnesium Stearate	0.5	0.5	0.8
Total	100	100	166.7
Capsule Shell	1	1	1
Capsule Size	#3	#3	#3

The celecoxib was milled by multiple passes through an oscillating mill fitted with successively smaller screen sizes (#14,#20, #40). The particle size of at least 90% of the celecoxib particles added to this mixture was less than

about 37 microns. Celecoxib, lactose and polyvinylpyrrolidone were mixed in a planetary mixer bowl and wet-granulated with water. The granulation was then tray dried at 60°C, milled through a 40 mesh screen, lubricated with magnesium stearate in a V-blender and encapsulated on a dosator-type encapsulator. The in vitro dissolution profile of the capsules was determined using USP method 2 and a dissolution media of a 15 mM phosphate buffer at pH 10. About 50% in vitro dissolution was achieved after about 15 minutes with greater than 95% in vitro dissolution after about 30 minutes.

The absorption, distribution, metabolism and elimination profile of this 100 mg dose capsule was compared to the profile of a suspension of [C^{14}]celecoxib. The study was an open-label, randomized crossover study carried out in ten healthy male subjects. The suspension was prepared by dissolving celecoxib in ethanol containing 5% polysorbate 80 and adding that mixture to apple juice prior to administration. Subjects receiving the suspension ingested a 300 mg dose of celecoxib. Subjects receiving capsule-form celecoxib received three 100 mg dose capsules for a total dose of 300 mg of celecoxib. The rate of absorption from the capsule was slower than from the suspension, but was equivalent to the suspension when measured by $AUC_{0\text{-}48\ hrs}$. Mean results are reported in Table 13B below. [C^{14}]Celecoxib was largely metabolized with only about 2.56% of the radioactive dose in either urine or feces.

Table 13B

PHARMACOKINETIC PARAMETER	**CELECOXIB SUSPENSION**	**CELECOXIB CAPSULES**
$AUC_{(0\text{-}48)}$ ((ng/ml)hr)	8706.7	8763.1
C_{max} (ng/ml)	1526.5	1076.5
T_{max} (hr)	1.42	1.94
$T_{1/2}$ (hr)	11.53	15.57

Exampl 14

Capsules having the following formulations were prepared and evaluated:

Table 14

INGREDIENT	AMOUNT (mg)	
	100 mg Capsule	200 mg Capsule
Celecoxib	100	200
Lactose	223.4	120.1
Povidone (K29-32)	8.3	8.3
Magnesium Stearate	1.7	5
Total	333.4	333.4
Capsule Size	#1	#1

These formulations were prepared in a manner similar to the formulations of Example 13 except that an inpact-type pin mill was used instead of an oscillating mill. Particle size was further reduced by use of the pin mill. For the 100 mg dose capsule about 30% in vitro dissolution was achieved after about 15 minutes with greater than 85% in vitro dissolution after about 30 minutes. For the 200 mg capsule about 50% in vitro dissolution was achieved after about 15 minutes with greater than 85% in vitro dissolution after about 30 minutes.

Example 15: Preparation of 100 mg Dose Capsules

The 100 mg dose and 200 mg dose capsules of Examples 1 and 2, respectively, can be prepared in accordance with acceptable pharmaceutical manufacturing practices in the manner illustrated by Figure 1 or Figure 2. The 100 mg dose and 200 mg dose tablets of Examples 3 and 4, respectively, can be prepared by appropriately modifying this process to account for the extragranular addition of croscarmellose sodium and microcrystalline cellulose, and tableting instead of encapsulating the composition.

An illustrative process for the bulk formulation of 100 mg dose capsules using the starting materials described below. A typical batch

consists of four identical granulation sections, although the number of granulation sections is not narrowly critical and depends largely upon equipment handling capacity and batch size needed.

Milling: The celecoxib was milled in an impact-type pin mill with counter rotating disks. At mill speeds ranging from about 8960 rpm/5600 rpm to about 11200 rpm/5600 rpm (rotating rpm/counter rotating rpm) particle size varied within relatively narrow ranges (at least 90% of the particles were 30 microns or less in size) suggesting that mill speed is not narrowly critical to the bulk drug micronization process. Figure 2 is a flow diagram showing a preferred embodiment wherein the celecoxib starting material is impact milled prior to blending with the carrier materials.

Dry Mixing: The celecoxib, lactose, Povidone and croscarmellose sodium were transferred to a 1200 L Niro Fielder PMA-1200 high speed granulator and mixed for about 3 minutes at fast chopper and impeller speeds. This dry mixing time provided adequate mixing of celecoxib with the carrier materials prior to the start of the wet granulation step.

Wet Granulation: Sodium lauryl sulfate (8.1 kg) was dissolved in purified USP water (23.7 kg). This solution was progressively added to the granulator at a rate of about 14 kg/minute. Total granulation time was about 6.5 minutes. During this granulation, the main blade and chopper blade of the granulator were placed on the fast speed setting. The wet granulated mixture was about 8.1% water by weight. Alternatively, the sodium lauryl sulfate can be mixed with the celecoxib, lactose, Povidone and croscarmellose sodium in the dry mixing step and purified USP water can be added to this dry mixture comprising sodium lauryl sulfate.

Drying: The wet granulation was delumped using a Quadro Comil Model 198 S screening mill equipped with rotating impeller and a coarse screen. Wet milling was used to eliminate large material lumps that formed as a by-product of the wet granulation operation. If not removed, these lumps would have prolonged the subsequent fluidized bed drying operation and increase the variation with respect to moisture control. The delumped granulation was transferred to an Aeromatic Fluid Bed Dryer T-8. The inlet air temperature

and flow rate were adjusted to about 60EC and about 5000 to 6000 ft^3/minute. The granulation was dried in the fluidized bed dryer to reduce the moisture content to between 0.5% to 2.5%. Moisture content was monitored using a Computrac Moisture Analyzer. Drying continued until the loss on drying of the granulation was not more than 1.0%. It may be desirable to combine two or more granulation sections for this drying step and subsequent processing steps.

Dry Milling: The dry granules were passed through a Fluid Air Mill Model 007 impact mill (conventional hammer) equipped with a 0.028 inch to 0.063 inch screen, knives forward, and 2400 rpm speed. Dry milling was used in combination with the wet granulation step to control the final size distribution of the granules.

Blending and Lubrication: The milled granules were then placed in a PK Cross-Flow Blender 75 Cubic Foot diffusion mixer/V- blender. The magnesium stearate was added and the mixture blended for about 5 minutes. The blending time provided blended material that was uniform with respect to the concentration of celecoxib. Blender rotational speed was 10.6 revolutions per minute. The final blend was used to combine materials from multiple granulation sections into a single uniform mixture and to evently distribute lubricant into the material prior to encapsulation into final dosage units.

Encapsulation: The granulated powder blend was encapsulated using an MG2 G100 encapsulator or an MG2 G120 encapsulator. The capsules were polished.

The above sequence of unit operations produced granules that were highly uniform in celecoxib content at the unit dose level, that readily dissolved in vitro, that flowed with sufficient ease so weight variation could be reliably controlled during capsule filling, and that were dense enough in bulk so that the batch could be processed in the selected equipment and individual doses fit into the specified capsules.

Exampl 16: Bio quivalency Study

The bioequivalency and safety of 200 mg doses of celecoxib were

evaluated in an open-label, randomized, single dose, three-way crossover study of a group of 46 healthy adult humans. The subjects received three single 200 mg doses celecoxib administered as (A) one 200 mg dose capsule, (B) two 100 mg dose capsules, (C) two 100 mg dose capsules (from a different batch run). Treatments were separated by seven days. The specific pharmaceutical compositions of the 100 mg dose capsule and the 200 mg dose capsules are disclosed in Examples 1 and 2, respectively. The subjects, who had fasted overnight, received single oral doses of the study medication together with about 180 mL of water at 0800 hours. The subjects continued to fast and remained in an upright position for four hours after dose administration. Blood samples were collected at -0.25 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose. Analyses of the separated plasma were performed at PPD Pharmaco, Richmond, VA. Celecoxib plasma concentrations were determined using a validated high performance liquid chromatography ("HPLC") procedure with a lower limit of detection of 10.0 ng/mL. Each subject was separately tested after receiving one 200 dose mg capsule and after receiving two 100 mg dose capsules. A minimum of a seven day wash-out period was allowed between administration of each single 200 mg dose. The mean results obtained from the 46 subjects tested are reported in Tables 16A and 16B below.

Table 16A

TIME (h_urs)	PLASMA CONCENTRATION OF CELECOXIB (ng/mL)		
	One 200 mg Dose Capsule (Example 2)	Two 100 mg Dose Capsules (Example 1--Batch 1)	Two 100 mg Dose Capsules (Example 1--Batch 2)
-0.25	0.22	0.00	0.00
0.5	103.74	117.89	212.61
1.0	418.24	446.39	647.00
1.5	575.68	606.97	826.90
2.0	646.83	656.98	862.23
3.0	686.19	666.55	781.13
4.0	621.02	595.21	660.15
6.0	389.00	387.41	383.81
8.0	322.24	332.51	323.59
12.0	214.63	208.06	209.96
16.0	149.11	146.40	144.23
24.0	116.09	111.77	113.21
36.0	52.76	48.27	46.98
48.0	27.24	26.47	22.44

Table 16B

PHARMACO-KINETIC PARAMETER	PHARMACOKINETIC PARAMETER VALUE		
	One 200 mg Dose Capsule (Example 2)	**Two 100 mg Dose Capsules (Example 1--Batch 1)**	**Two 100 mg Dose Capsules (Example 1--Batch 2)**
$AUC_{(0\text{-}48)}$ ((ng/mL)hr)	8107.07	7976.56	8535.49
$AUC_{(0\text{-}LQC)}$ ((ng/mL)hr)	8063.17	7953.71	8501.94
$AUC_{(0\text{-}\infty\ hours)}$ ((ng/mL)hr)	8828.64	8640.46	9229.52
C_{max} (mg/mL)	801.19	815.21	959.50
T_{max} (hours)	2.46	2.84	2.23
$T_{1/2}$ (hours)	12.22	13.52	10.67
$C_{max}/AUC_{(0\text{-}LQC)}$	0.10	0.10	0.20

Example 17: Effect of Food Study

An open-label randomized, single dose, four-way crossover study was employed to evaluate the dose proportionality and the effect of food on the pharmacokinetic profile of celecoxib in healthy adult subjects. Safety was assessed based on adverse events, vital signs and clinical laboratory tests. Twenty four healthy adult subjects were randomized to receive the following single doses of celecoxib: (A) a 50 mg dose capsule under fasting conditions, (B) a 50 mg dose capsule immediately following a high fat breakfast, (C) a 100 mg dose capsule under fasting conditions, and (D) a 100 mg dose capsule immediately following a high fat breakfast. The subjects received the study medication on days 1, 8, 15, and 22 in one of four treatment sequences

(ADBC; BACD; CBDA; and DCAB). The specific composition of the 100 mg dose capsule is disclosed in Example 1. The specific composition of the 50 mg dose capsule is disclosed in Table 17A below:

Table 17A

INGREDIENT	**Amount (mg)**
Celecoxib	50.00
Lactose Monohydrate	199.8
Sodium Lauryl Sulfate	8.1
Povidone (K29-32)	6.8
Croscarmellose Sodium	2.7
Magnesium Stearate	2.7
Total Capsule Fill Weight	270.0

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2).

Blood samples were collected at -0.25 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose. Analyses of the separated plasma were performed at PPD Pharmaco, Richmond, VA. Celecoxib plasma concentrations were determined using a validated high performance liquid chromatography ("HPLC") procedure with a lower limit of detection of 10.0 ng/mL. There were no clinically significant changes in vital signs or physical examinations. All adverse events were mild in severity. The mean results obtained from the 24 subjects tested are reported in Tables 17B and 17C below.

Table 17B

TIME (Hours)	PLASMA CONCENTRATION OF CELECOXIB (ng/mL)			
	Single 100 mg dose capsule (fasting)	**Single 100 mg dose capsule (high fat breakfast)**	**Single 50 mg dose capsule (fasting)**	**Single 50 mg dose capsule (high fat breakfast)**
-0.25	0.00	0.00	0.00	0.00
0.5	63.96	1.35	52.90	2.38
1.0	225.65	14.00	155.07	11.98
1.5	344.77	49.37	202.22	29.85
2.0	354.45	139.43	220.15	63.00
3.0	348.03	438.99	253.85	186.94
4.0	333.86	600.00	244.80	298.23
6.0	196.53	355.65	118.58	188.90
8.0	152.35	314.54	91.79	165.85
12.0	121.08	179.04	61.13	88.76
16.0	86.13	102.12	39.51	51.86
24.0	61.77	49.31	28.22	22.81
36.0	38.00	17.88	10.69	8.75
48.0	17.77	7.91	5.77	3.80

Table 17C

PHARMACO-KINETIC PARAMETER	PHARMACOKINETIC PARAMETER VALUE			
	Single 100 dose mg capsule (fasting)	**Single 100 mg dose capsule (high fat breakfast)**	**Single 50 mg dose capsule (fasting)**	**Single 50 mg dose capsule (high fat breakfast)**
$AUC_{(0\text{-}48)}$ ((ng/mL)hr)	4463.28	5214.86	2426.23	2601.10
$AUC_{(0\text{-}LQC)}$ ((ng/mL)hr)	4415.59	5105.50	2352.68	2501.56
$AUC_{(0\text{-}\infty\ hours)}$ ((ng/mL)hr)	5126.74	5419.21	2693.80	2759.42
C_{max} (mg/mL)	455.00	746.96	321.46	354.17
T_{max} (hours)	2.60	5.00	2.92	4.46
$T_{1/2}$ (hours)	16.02	6.86	11.01	6.49
$C_{max}/AUC_{(0\text{-}LQC)}$	0.11	0.15	0.16	0.16

Example 18: Suspension Versus Capsule

The phamacokinetics and bioavailability of an oral fine suspension and two oral capsules containing of celecoxib were evaluated in an open-label, randomized, single dose, crossover study. Thirty six healthy adult subjects were randomized to receive the following single doses of celecoxib: (A) one 200 mg dose capsule, (B) two 100 mg dose capsules, and (C) a 200 mg oral fine suspension. The entire treatment duration was 18 days. On days 1, 8 and 15 the subjects received one of the three treatments according to a randomization schedule. Treatments were separated by seven days. The specific pharmaceutical composition of the 200 mg dose capsule is disclosed in Example 2. The specific pharmaceutical composition of the 100 mg dose capsules is disclosed in Table 18A below.

Table 18A

INGREDIENT	AMOUNT (mg)	WEIGHT PERCENT
Celecoxib	100.0	60.0
Lactose Monohydrate	61.7	37.0
Povidone, K29-32	4.20	2.51
Magnesium Stearate	0.80	0.48

The pharmaceutical composition used in the 100 mg dose capsules was prepared by passing the celecoxib starting material through a 40 mesh oscillating screen (no other milling was performed), wet granulating the celecoxib, lactose and povidone in a low shear planetary mixer, tray drying and milling the granulated mixture, adding magnesium stearate to the granulated mixture and blending to form the final pharmaceutical composition.

The oral fine suspension was prepared by dissolving celecoxib in ethanol containing 5% polysorbate 80 and adding that mixture to apple juice prior to administration.

Blood samples were collected at -0.25 (predose) and through 72 hours post dose. Each subject was separately tested after receiving the 200 dose mg capsule, 100 mg dose capsules and oral fine suspension. A minimum of a seven day wash-out period was allowed between administration of each 200 mg dose. The mean results obtained from the 36 subjects tested are reported in Table 18B below.

Table 18B

PHARMACO-KINETIC PARAMETER	PHARMACOKINETIC PARAMETER VALUE		
	Two 100 mg Dose Capsules	One 200 mg Dose Capsules	200 mg Oral Fine Solution
AUC $_{(0-72)}$ ((ng/mL)hr)	7247.5 ± 2427.5	7648.1 ± 2412.1	7736.2 ± 2488.2
C_{max} (mg/mL)	619.7 ± 249.4	704.6 ± 265.7	1228.8 ± 452.0
T_{max} (hours)	3.00 ± 0.99	2.83 ± 1.06	0.79 ± 0.32
$T_{1/2}$ (hours)	13.96 ± 5.27	11.92 ±3.60	13.33 ± 6.69
$AUC_{(0-\infty)}$ (ng/mL)hr	7562.4 ± 2494.0	7830.3 ± 2448.4	8001.2 ± 2535.6
$CL_{(0-72)}$ (L/hr)	30.4 ± 9.8	28.4 ± 7.8	28.1 ± 7.8

In general, the rate of celecoxib absorption was greater for the oral fine suspension (higher C_{max} and shorter T_{max}) than for the capsules. The overall extent of celecoxib absorption for the oral fine suspension, however, was similar to the overall extent of celecoxib absorption for the capsules.

As various changes could be made in the above formulations and methods without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense. All mentioned references are incorporated by reference as if here written. When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

What is claimed is:

Sub B1

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib characterized by at least one of

(a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;

(b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;

(c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;

(d) a terminal half-life ($T_{1/2}$) not less than about 10 h; and

(e) a maximum concentration (C_{max}) not less than about 200 ng/ml.

2. A composition of Claim 1 wherein the time course of blood serum concentration of celecoxib is characterized by a T_{max} not greater than about 3 h, preferably not greater than about 2 h, and more preferably not greater than about 1.7 h, after administration.

3. A composition of Claim 1 wherein the C_{max} is not less than about 200 ng/ml, preferably not less than about 400 ng/ml.

4. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having relative bioavailability not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution containing an equivalent amount of celecoxib.

5. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one

or more pharmaceutically acceptable excipients, and having a distribution of celecoxib particle sizes such that at least 90% of particles are smaller than 200 μm, preferably smaller than 100 μm, more preferably smaller than 40 μm, and most preferably smaller than 25 μm, in the longest dimension of said particles.

6. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a mean celecoxib particle size of about 1 μm to about 10 μm.

7. A composition of any of Claims 1 to 6 wherein the amount of celecoxib in each dose unit is about 50 mg to about 800 mg, preferably about 75 mg to about 400 mg, and more preferably about 100 mg to about 200 mg.

8. A composition of any of Claims 1 to 7 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for providing therapeutically or prophylactically effective inhibition of cyclooxygenase-2.

9. A composition of any of Claims 1 to 7 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for treatment or prophylaxis of a cyclooxygenase-2 mediated condition or disorder.

10. A composition of any of Claims 1 to 9 wherein said dose units are in a form of discrete solid articles.

11. A composition of Claim 10 wherein said articles are tablets, pills, hard or soft capsules, lozenges, sachets or pastilles.

12. A composition of Claim 10 in the form of unit dosage capsules or tablets.

13. A composition of Claim 12 wherein said excipients are selected from the group consisting of pharmaceutically acceptable diluents,

disintegrants, binding agents, wetting agents and lubricants.

14. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable diluents in a total amount of about 5% to about 99% by weight, preferably about 10% to about 85% by weight, of the composition.

15. A composition of Claim 14 wherein said diluents are selected from the group consisting of lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, Celutab, inositol, hydrolyzed cereal solids, amylose, Rexcel, powdered cellulose, calcium carbonate, glycine and bentonite.

16. A composition of Claim 14 wherein said diluents are selected from the group consisting of lactose and microcrystalline cellulose.

17. A composition of Claim 14 wherein said diluents comprise lactose.

18. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable disintegrants in a total amount of about 0.2% to about 30% by weight, preferably about 0.2% to about 10% by weight, of the composition.

19. A composition of Claim 18 wherein said disintegrants are selected from the group consisting of starches, sodium starch glycolate, clays, celluloses, alginates, pregelatinized corn starches, crospovidone and gums.

20. A composition of Claim 18 wherein said disintegrants comprise croscarmellose sodium.

21. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable binding agents in a total amount of about 0.5% to about 25% by weight, preferably about 0.75% to about 15% by weight, of the composition.

22. A composition of Claim 21 wherein said binding agents are selected

from the group consisting of acacia, tragacanth, sucrose, gelatin, glucose, starch, celluloses, methylcellulose, sodium carboxymethylcellulose, alginic acid and salts thereof, magnesium aluminum silicate, polyethylene glycols, guar gum, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose and pregelatinized starch.

23. A composition of Claim 21 wherein said binding agents comprise polyvinylpyrrolidone.

24. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable wetting agents in a total amount of about 0.25% to about 15% by weight, preferably about 0.4% to about 10% by weight, of the composition.

25. A composition of Claim 24 wherein said wetting agents comprise an anionic surfactant, preferably sodium lauryl sulfate.

26. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable lubricants in a total amount of about 0.1% to about 10% by weight, preferably about 0.2% to about 8% by weight, of the composition.

27. A composition of Claim 26 wherein said lubricants are selected from the group consisting of glyceryl behapate, stearates, stearic acid, hydrogenated vegetable oils, talc, waxes, Stearowet, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, polyethylene glycols, sodium oleate, sodium lauryl sulfate and magnesium lauryl sulfate.

28. A composition of Claim 26 wherein said lubricants comprise magnesium stearate.

29. A composition of Claim 12 comprising

(a) one or more pharmaceutically acceptable diluents in a total amount of about 10% to about 85% by weight of the composition;

(b) one or more pharmaceutically acceptable disintegrants in a total amount of about 0.2% to about 10% by weight of the composition; and

(c) one or more pharmaceutically acceptable binding agents in an amount of about 0.5% to about 10% by weight of the composition.

30. A composition of Claim 29 further comprising (d) one or more pharmaceutically acceptable wetting agents in a total amount of about 0.4% to about 10% by weight of the composition.

31. A composition of Claim 29 or Claim 30 further comprising (e) one or more pharmaceutically acceptable lubricants in a total amount of about 0.2% to about 8% by weight of the composition.

32. A composition of any of Claims 29 to 31 wherein said diluents comprise lactose.

33. A composition of any of Claims 29 to 32 wherein said disintegrants comprise croscarmellose sodium.

34. A composition of any of Claims 29 to 33 wherein said binding agents comprise polyvinylpyrrolidone.

35. A composition of any of Claims 30 to 34 wherein said wetting agents comprise sodium lauryl sulfate.

36. A composition of any of Claims 31 to 35 wherein said lubricants comprise magnesium stearate.

37. A composition of any of Claims 12 to 36 wherein celecoxib is present in an amount of about 1% to about 95% by weight, preferably about 25% to about 85% by weight, of the composition.

38. A composition of Claim 12 comprising

(a) about 1 to about 95 weight percent of celecoxib;

(b) about 5 to about 99 weight percent of lactose;

(c) about 2 to about 10 weight percent of croscarmellose sodium;

(d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone;

(e) 0 to about 7 weight percent of sodium lauryl sulfate; and

(f) 0 to about 5 weight percent of magnesium stearate.

39. A composition of Claim 12 comprising

(a) about 25 to about 85 weight percent of celecoxib;

(b) about 5 to about 70 weight percent of lactose;

(c) about 0.2 to about 6 weight percent of croscarmellose sodium;

(d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone;

(e) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and

(f) about 0.2 to about 8 weight percent of magnesium stearate.

40. A composition of Claim 12 comprising

(a) about 27 to about 47 weight percent of celecoxib;

(b) about 45 to about 65 weight percent of lactose;

(c) about 0.5 to about 5 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

41. A composition of Claim 12 comprising

(a) about 32 to about 42 weight percent of celecoxib;

(b) about 50 to about 60 weight percent of lactose;

(c) about 0.5 to about 3 weight percent of croscarmellose sodium;

(d) about 1 to about 5 weight percent of polyvinylpyrrolidone; and

(e) about 0.4 to about 6 weight percent of sodium lauryl sulfate.

42. A composition of Claim 12 comprising

(a) about 35 to about 39 weight percent of celecoxib;

(b) about 54 to about 57 weight percent of lactose;

(c) about 0.5 to about 2 weight percent of croscarmellose sodium;

(d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;

(e) about 2 to about 4 weight percent of sodium lauryl sulfate; and

(f) about 0.5 to about 2 weight percent of magnesium stearate.

43. A composition of Claim 12 comprising

(a) about 65 to about 85 weight percent of celecoxib;

(b) about 8 to about 28 weight percent of lactose;

(c) about 0.5 to about 5 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

44. A composition of Claim 12 comprising

(a) about 69 to about 79 weight percent of celecoxib;

(b) about 13.5 to about 23.5 weight percent of lactose;

(c) about 0.5 to about 3 weight percent of croscarmellose sodium;

(d) about 1 to about 5 weight percent of polyvinylpyrrolidone; and

(e) about 0.4 to about 6 weight percent of sodium lauryl sulfate.

45. A composition of Claim 12 comprising

(a) about 72 to about 76 weight percent of celecoxib;

(b) about 16.5 to about 20.5 weight percent of lactose;

(c) about 0.5 to about 2 weight percent of croscarmellose sodium;

(d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;

(e) about 2 to about 4 weight percent of sodium lauryl sulfate; and

(f) about 0.5 to about 2 weight percent of magnesium stearate.

46. A composition of Claim 12 comprising

(a) about 30 to about 50 weight percent of celecoxib;

(b) about 30 to about 50 weight percent of lactose;

(c) about 0.5 to about 10 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

47. A composition of Claim 12 comprising

(a) about 35 to about 45 weight percent of celecoxib;

(b) about 35 to about 45 weight percent of lactose;

(c) about 1 to about 5 weight percent of croscarmellose sodium;

(d) about 1 to about 5 weight percent of polyvinylpyrrolidone; and

(e) about 5 to about 15 weight percent of microcrystalline cellulose.

48. A composition of Claim 12 comprising

(a) about 38 to about 42 weight percent of celecoxib;

(b) about 38 to about 42 weight percent of lactose;

(c) about 1.5 to about 4.5 weight percent of croscarmellose sodium;
(d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;
(e) about 8 to about 12 weight percent of microcrystalline cellulose;
(f) about 2 to about 4 weight percent of sodium lauryl sulfate; and
(g) about 0.5 to about 2 weight percent of magnesium stearate.

49. A composition of Claim 12 comprising, in each dose unit,
(a) about 80 to about 220 mg of celecoxib;
(b) about 30 to about 225 mg of lactose;
(c) about 0.5 to about 25 mg of croscarmellose sodium;
(d) about 0.5 to about 25 mg of polyvinylpyrrolidone;
(e) 0 to about 70 mg of microcrystalline cellulose;
(f) 0 to about 25 mg of sodium lauryl sulfate; and
(g) 0 to about 10 mg of magnesium stearate.

50. A composition of Claim 12 comprising unit dosage capsules each containing
(a) about 100 mg of celecoxib;
(b) about 149.75 mg of lactose monohydrate;
(c) about 2.7 mg of croscarmellose sodium;
(d) about 6.75 mg of polyvinylpyrrolidone;
(e) about 8.1 mg of sodium lauryl sulfate; and
(f) about 2.7 mg of magnesium stearate.

51. A composition of Claim 12 comprising unit dosage capsules each containing
(a) about 200 mg of celecoxib;
(b) about 49.75 mg of lactose monohydrate;
(c) about 2.7 mg of croscarmellose sodium;
(d) about 6.75 mg of polyvinylpyrrolidone;
(e) about 8.1 mg of sodium lauryl sulfate; and
(f) about 2.7 mg of magnesium stearate.

51. A composition of Claim 12 comprising unit dosage tablets each containing

(a) about 100 mg of celecoxib;
(b) about 101.88 mg of lactose monohydrate;
(c) about 7.5 mg of croscarmellose sodium;
(d) about 6.25 mg of polyvinylpyrrolidone;
(e) about 25 mg of microcrystalline cellulose;
(f) about 7.5 mg of sodium lauryl sulfate; and
(g) about 1.88 mg of magnesium stearate.

52. A composition of Claim 12 comprising unit dosage tablets each containing
(a) about 200 mg of celecoxib;
(b) about 203.8 mg of lactose monohydrate;
(c) about 15 mg of croscarmellose sodium;
(d) about 12.5 mg of polyvinylpyrrolidone;
(e) about 50 mg of microcrystalline cellulose;
(f) about 15 mg of sodium lauryl sulfate; and
(g) about 3.75 mg of magnesium stearate. .

53. A composition of Claim 12 comprising unit dosage capsules or tablets each providing a 100 mg or 200 mg dose of celecoxib.

54. A composition of Claim 12 wherein the celecoxib, together with one or more excipients, is directly encapsulated or directly compressed into tablets.

55. A composition of Claim 12 wherein the celecoxib, together with one or more excipients, is wet granulated prior to encapsulation or compression into tablets.

56. A composition of Claim 12 wherein the celecoxib, together with one or more excipients, is dry granulated prior to encapsulation or compression into tablets.

57. A composition of any of Claims 1 to 9 that is a substantially homogeneous flowable mass from which single dose units are measurably removable.

58. A composition of Claim 57 wherein said flowable mass is a particulate or granular solid.

59. A composition of Claim 57 wherein said flowable mass is a suspension having the celecoxib in a solid particulate phase dispersed in an aqueous phase.

60. A composition of Claim 59 wherein said excipients include a pharmaceutically acceptable wetting agent.

61. A composition of Claim 60 wherein said wetting agent is polysorbate 80.

62. A composition of Claim 60 or 61 further comprising a solvent from which the celecoxib is precipitated to prepare the suspension.

63. A composition of Claim 62 wherein said solvent is an alcohol, preferably ethanol.

64. A composition of Claim 59 wherein the aqueous phase comprises a palatable vehicle selected from the group consisting of water, syrup and fruit juice.

65. A composition of Claim 64 wherein the vehicle is fruit juice, preferably apple juice.

66. A composition of any of Claims 1 to 65 providing, upon oral ingestion, a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 h after ingestion.

67. A composition of Claim 66 wherein the therapeutic effect is provided over an interval of about 24 h after ingestion.

68. A composition of any of Claims 1 to 65 wherein, upon oral ingestion, at least about 50% of the celecoxib is released, as determined in vitro, within about 15 minutes after ingestion.

69. A composition of any of Claims 1 to 68 further comprising one or more opioid or analgesic drugs.

70. A composition of Claim 69 wherein said opioid or analgesic drugs are

selected from the group consisting of narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers.

71. A composition of Claim 69 wherein said opioid or analgesic drugs are selected from the group consisting of morphine, meperidine, codeine, pentacozine, buprenorphine, butorphanol, dexocine, meptazinol, hydrocodone, oxycodone, methadone, Tramadol, including racemate and single enantiomers thereof, DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetaminophen, propoxyphene, nalbuphene, E-4018, filenadol, mirfentanil, amitriptyline, DuP 631, GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, AXC-3742, SNX-111, ADL2-1294, CT-3 and CP-99994.

72. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a composition of any of Claims 1 to 71 once or twice a day.

73. A method of Claim 72 wherein the condition or disorder is rheumatoid arthritis.

74. A method of Claim 72 wherein the condition or disorder is osteoarthritis.

75. A method of Claim 72 wherein the condition or disorder, or a symptom of the condition or disorder, is pain.

76. A method of use of a composition of any of Claims 1 to 9 in the manufacture of a medicament for the treatment or prophylaxis of a cyclooxygenase-2 mediated condition or disorder.

77. A method of Claim 76 wherein the condition or disorder is rheumatoid arthritis.

78. A method of Claim 76 wherein the condition or disorder is osteoarthritis.

79. A method of Claim 76 wherein the condition or disorder, or a symptom of the condition or disorder, is pain.

80. A method of preparing a composition of Claim 12 comprising
    (a) wet granulating celecoxib together with one or more excipients to form a wet granulated mixture;
    (b) drying the wet granulated mixture; and
    (c) encapsulating the dried granulated mixture or compressing the dried granular mixture into tablets.

81. A method of Claim 80 wherein, prior to the wet granulating step, the celecoxib is milled such that at least 90% of the resulting particles are smaller than 200 μm, preferably smaller than 100 μm, more preferably smaller than 40 μm, and most preferably smaller than 25 μm, in the longest dimension of said particles.

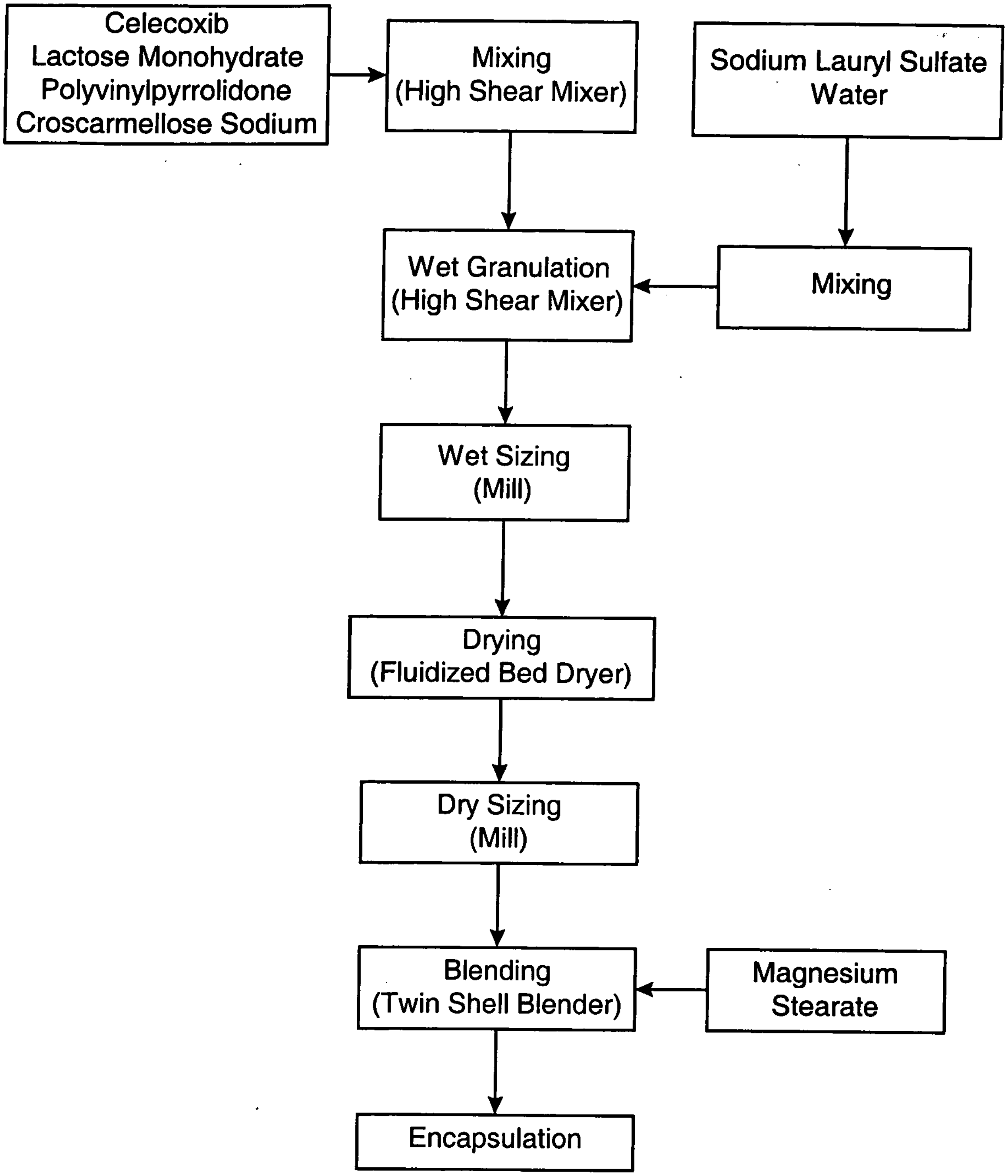
82. A method of Claim 81 wherein said milling is performed with a pin mill to provide celecoxib particles, at least 90% of which are smaller than 25 μm, in the longest dimension of said particles.

83. A method of Claim 82 wherein said milling results in a mean celecoxib particle size of about 1 μm to about 10 μm, preferably about 5 μm to about 7 μm.

Abstract of th Discl sur

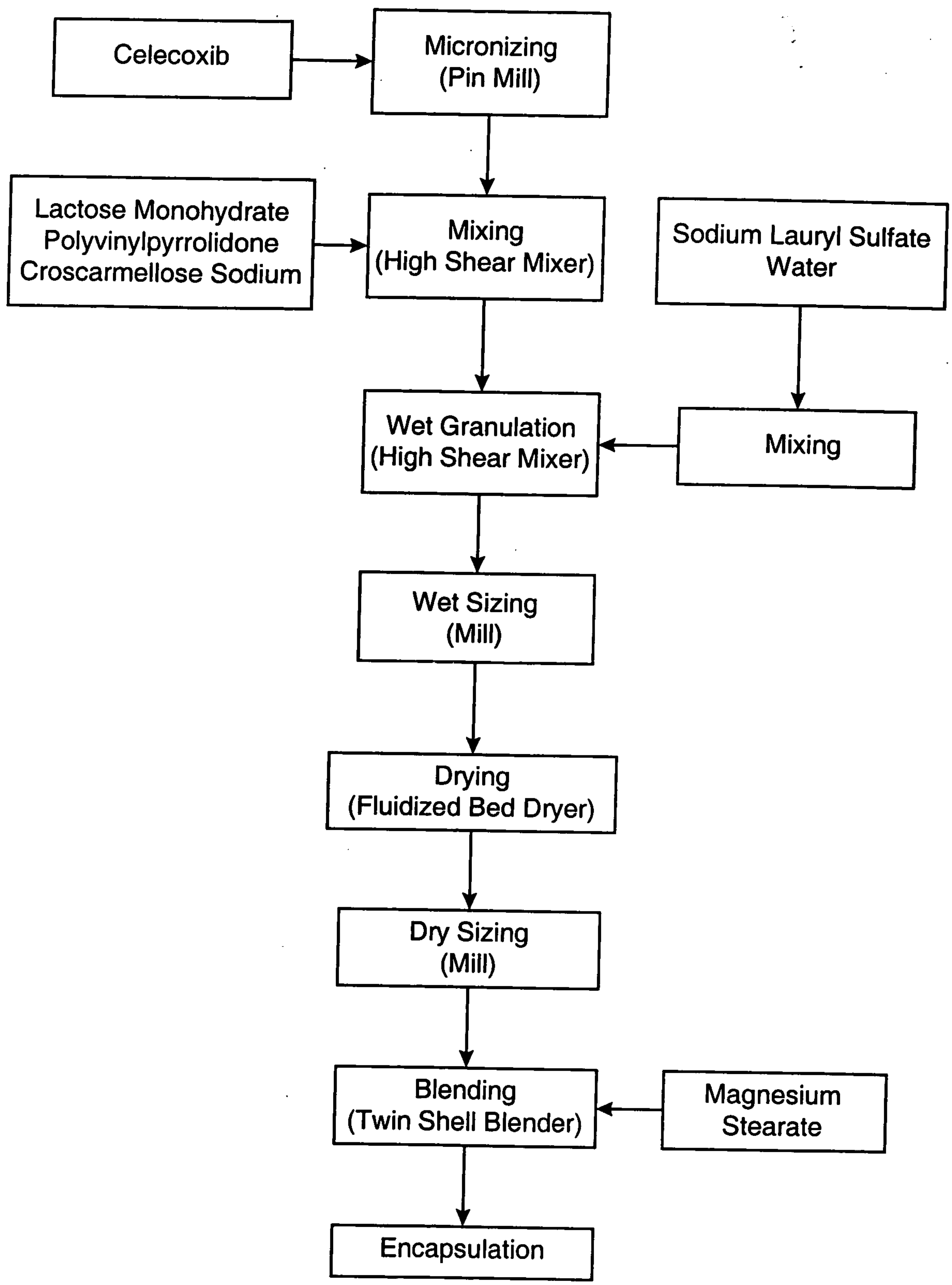
Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.

SHEET 1 OF 2



Figur 1

SHEET 2 OF 2



Figur 2